

WEBVTT

NOTE duration:"01:06:48"

NOTE recognizability:0.923

NOTE language:en-us

NOTE Confidence: 0.857201046666667

00:00:00.000 --> 00:00:01.959 All right. Welcome

NOTE Confidence: 0.95786455

00:00:01.960 --> 00:00:05.680 everyone. Thanks for coming today.

NOTE Confidence: 0.95786455

00:00:05.680 --> 00:00:10.090 It is my honor to introduce my friend

NOTE Confidence: 0.95786455

00:00:10.090 --> 00:00:13.420 and mentor and fellow neuropathologist,

NOTE Confidence: 0.95786455

00:00:13.420 --> 00:00:15.520 Doctor Jeffrey Golden.

NOTE Confidence: 0.95786455

00:00:15.520 --> 00:00:17.718 Some of you may know Jeff is

NOTE Confidence: 0.95786455

00:00:17.718 --> 00:00:20.237 actually my PhD mentor and advisor

NOTE Confidence: 0.95786455

00:00:20.237 --> 00:00:22.237 at University of Pennsylvania.

NOTE Confidence: 0.95786455

00:00:22.240 --> 00:00:24.160 He's currently the director of

NOTE Confidence: 0.95786455

00:00:24.160 --> 00:00:26.080 the Burns and Allen Research.

NOTE Confidence: 0.95786455

00:00:26.080 --> 00:00:28.816 Institute at Cedars Sinai and also the Vice

NOTE Confidence: 0.95786455

00:00:28.816 --> 00:00:31.719 Dean of Research and Graduate Education.

NOTE Confidence: 0.95786455

00:00:31.720 --> 00:00:33.730 Jeff I graduated from University

NOTE Confidence: 0.95786455

00:00:33.730 --> 00:00:35.740 of Pennsylvania School of Medicine
NOTE Confidence: 0.95786455

00:00:35.800 --> 00:00:38.236 and after that went on to do
NOTE Confidence: 0.95786455

00:00:38.236 --> 00:00:39.280 his neuropathology fellowship
NOTE Confidence: 0.95786455

00:00:39.280 --> 00:00:42.717 and and postdoc training at MGH.
NOTE Confidence: 0.95786455

00:00:42.717 --> 00:00:45.216 And he did his postdoc in Connie
NOTE Confidence: 0.95786455

00:00:45.216 --> 00:00:47.324 Sepco's lab and really launched
NOTE Confidence: 0.95786455

00:00:47.324 --> 00:00:49.652 his career into studying the
NOTE Confidence: 0.95786455

00:00:49.652 --> 00:00:52.072 cellular and molecular basis of
NOTE Confidence: 0.95786455

00:00:52.072 --> 00:00:53.040 neurodevelopmental disorders.
NOTE Confidence: 0.95786455

00:00:53.040 --> 00:00:54.598 He did.
NOTE Confidence: 0.95786455

00:00:54.598 --> 00:00:56.788 Really pioneering work studying non
NOTE Confidence: 0.95786455

00:00:56.788 --> 00:00:59.463 radial cell migration and its critical
NOTE Confidence: 0.95786455

00:00:59.463 --> 00:01:02.090 role in interneuron migration during
NOTE Confidence: 0.95786455

00:01:02.090 --> 00:01:04.790 neocortical development and his
NOTE Confidence: 0.95786455

00:01:04.790 --> 00:01:07.644 research has made he's made really
NOTE Confidence: 0.95786455

00:01:07.644 --> 00:01:09.148 many contributions in understanding

NOTE Confidence: 0.95786455

00:01:09.148 --> 00:01:11.466 the molecular and cellular basis of

NOTE Confidence: 0.95786455

00:01:11.466 --> 00:01:13.890 several malformations of cortical

NOTE Confidence: 0.95786455

00:01:13.890 --> 00:01:16.410 development as well as epilepsy and

NOTE Confidence: 0.95786455

00:01:16.410 --> 00:01:21.630 and other intellectual disorders. So I.

NOTE Confidence: 0.95786455

00:01:21.630 --> 00:01:23.390 Won't really take up any more time,

NOTE Confidence: 0.93773775

00:01:24.030 --> 00:01:25.230 but it's it's just

NOTE Confidence: 0.935940714285714

00:01:26.070 --> 00:01:27.988 such an honor to have Jeff here.

NOTE Confidence: 0.935940714285714

00:01:27.990 --> 00:01:29.310 We've been trying to get him here

NOTE Confidence: 0.935940714285714

00:01:29.310 --> 00:01:31.710 since before the pandemic and so

NOTE Confidence: 0.935940714285714

00:01:31.710 --> 00:01:33.494 finally he's here. I'm so pleased.

NOTE Confidence: 0.935940714285714

00:01:33.494 --> 00:01:35.270 Please join me in welcoming him.

NOTE Confidence: 0.9320542222222222

00:01:39.990 --> 00:01:41.622 Well, first, thank you,

NOTE Confidence: 0.9320542222222222

00:01:41.622 --> 00:01:43.662 Paula V for the invitation.

NOTE Confidence: 0.9320542222222222

00:01:43.670 --> 00:01:46.158 This is I think the third of several

NOTE Confidence: 0.9320542222222222

00:01:46.158 --> 00:01:47.550 aborted attempts to get here.

NOTE Confidence: 0.9320542222222222

00:01:47.550 --> 00:01:49.694 And so I'm really pleased to be here.
NOTE Confidence: 0.9320542222222222

00:01:49.700 --> 00:01:51.660 And actually since the pandemic,
NOTE Confidence: 0.9320542222222222

00:01:51.660 --> 00:01:53.220 this is I think the only,
NOTE Confidence: 0.9320542222222222

00:01:53.220 --> 00:01:55.497 this is only my second visit to a university,
NOTE Confidence: 0.9320542222222222

00:01:55.500 --> 00:01:58.034 so it's great to see people in
NOTE Confidence: 0.9320542222222222

00:01:58.034 --> 00:02:00.490 person and be able to start feeling
NOTE Confidence: 0.9320542222222222

00:02:00.490 --> 00:02:02.620 like we're getting back to normal.
NOTE Confidence: 0.9320542222222222

00:02:02.620 --> 00:02:04.660 So today what I want to
NOTE Confidence: 0.9320542222222222

00:02:04.660 --> 00:02:06.740 do is take you through
NOTE Confidence: 0.9452853

00:02:09.780 --> 00:02:11.220 we've been doing over.
NOTE Confidence: 0.95635504

00:02:28.560 --> 00:02:30.040 Technology have started to really
NOTE Confidence: 0.9352219

00:02:32.160 --> 00:02:32.840 just out
NOTE Confidence: 0.80314445

00:02:35.040 --> 00:02:35.120 there
NOTE Confidence: 0.926416425

00:02:38.340 --> 00:02:41.035 we go. So I like to start
NOTE Confidence: 0.926416425

00:02:41.035 --> 00:02:42.059 out there was playing
NOTE Confidence: 0.94226628

00:02:44.980 --> 00:02:46.420 that's good okay there we

NOTE Confidence: 0.881803616363636
00:02:48.700 --> 00:02:51.780 go case and and what you see here is a mom
NOTE Confidence: 0.934503085714286
00:02:54.820 --> 00:02:58.026 playing with her son in a crib.
NOTE Confidence: 0.934503085714286
00:02:58.030 --> 00:03:00.271 The sun has a cap on which is an
NOTE Confidence: 0.934503085714286
00:03:00.271 --> 00:03:02.427 EEG recording is a video EEG and
NOTE Confidence: 0.934503085714286
00:03:02.427 --> 00:03:04.781 and you see him almost kind of
NOTE Confidence: 0.934503085714286
00:03:04.781 --> 00:03:06.905 flop over as if almost playing.
NOTE Confidence: 0.934503085714286
00:03:06.910 --> 00:03:10.385 But in fact this is a what's called
NOTE Confidence: 0.934503085714286
00:03:10.385 --> 00:03:12.950 a drop seizure or a epileptic
NOTE Confidence: 0.934503085714286
00:03:12.950 --> 00:03:16.150 seizure that this child has.
NOTE Confidence: 0.934503085714286
00:03:16.150 --> 00:03:19.518 And the type of seizure actually pretends
NOTE Confidence: 0.934503085714286
00:03:19.518 --> 00:03:23.186 a very poor prognosis for this individual.
NOTE Confidence: 0.934503085714286
00:03:23.190 --> 00:03:26.414 This child will and actually did go on.
NOTE Confidence: 0.934503085714286
00:03:26.420 --> 00:03:29.900 To have a variety of different types of
NOTE Confidence: 0.934503085714286
00:03:29.900 --> 00:03:33.036 seizures and became increasingly severe.
NOTE Confidence: 0.934503085714286
00:03:33.036 --> 00:03:35.058 Also had cognitive
NOTE Confidence: 0.962057633333333

00:03:37.140 --> 00:03:39.540 disabilities and had
NOTE Confidence: 0.9620576333333333

00:03:39.540 --> 00:03:41.940 autism spectrum disorder.
NOTE Confidence: 0.9620576333333333

00:03:41.940 --> 00:03:43.780 And so from this very simple thing we
NOTE Confidence: 0.905285902105263

00:03:51.540 --> 00:03:53.908 neurobiology that must underlie.
NOTE Confidence: 0.905285902105263

00:03:53.908 --> 00:03:57.460 These defects and and that's really
NOTE Confidence: 0.905285902105263

00:03:57.548 --> 00:04:00.098 what I've been thinking about for
NOTE Confidence: 0.905285902105263

00:04:00.098 --> 00:04:01.884 most of my scientific career.
NOTE Confidence: 0.905285902105263

00:04:01.884 --> 00:04:03.900 So let me just tell you a couple
NOTE Confidence: 0.905285902105263

00:04:03.954 --> 00:04:05.616 basic things about epilepsy and then
NOTE Confidence: 0.905285902105263

00:04:05.616 --> 00:04:07.420 we'll get into some other things.
NOTE Confidence: 0.905285902105263

00:04:07.420 --> 00:04:09.304 It's actually pretty common.
NOTE Confidence: 0.905285902105263

00:04:09.304 --> 00:04:11.659 It's more common than stroke,
NOTE Confidence: 0.905285902105263

00:04:11.660 --> 00:04:13.820 which we hear about a lot.
NOTE Confidence: 0.905285902105263

00:04:13.820 --> 00:04:17.660 It is actually about as prevalent as asthma,
NOTE Confidence: 0.905285902105263

00:04:17.660 --> 00:04:19.658 which is heard about a lot.
NOTE Confidence: 0.905285902105263

00:04:19.660 --> 00:04:24.704 So epilepsy is a major healthcare issue.

NOTE Confidence: 0.905285902105263
00:04:24.704 --> 00:04:29.036 And it's really hard to control.
NOTE Confidence: 0.58313337
00:04:32.240 --> 00:04:38.500 Most Asian even with extensive
NOTE Confidence: 0.58313337
00:04:38.500 --> 00:04:41.744 multi drug therapy do not come under
NOTE Confidence: 0.58313337
00:04:41.744 --> 00:04:44.558 control and only a subset of them
NOTE Confidence: 0.58313337
00:04:44.558 --> 00:04:47.351 are able to be managed with surgery.
NOTE Confidence: 0.58313337
00:04:47.360 --> 00:04:48.392 So there are some that can
NOTE Confidence: 0.58313337
00:04:48.392 --> 00:04:49.080 be managed with surgery,
NOTE Confidence: 0.58313337
00:04:49.080 --> 00:04:51.110 but it's just a subset.
NOTE Confidence: 0.58313337
00:04:51.110 --> 00:04:54.030 So really we need to develop a
NOTE Confidence: 0.58313337
00:04:54.030 --> 00:04:56.430 far better understanding of the,
NOTE Confidence: 0.58313337
00:04:56.430 --> 00:04:58.510 the underlying biology to
NOTE Confidence: 0.58313337
00:04:58.510 --> 00:05:01.110 really begin to think about
NOTE Confidence: 0.58313337
00:05:01.110 --> 00:05:01.917 biologically relevant therapeutics.
NOTE Confidence: 0.58313337
00:05:01.917 --> 00:05:03.531 So we can talk about that
NOTE Confidence: 0.58313337
00:05:03.531 --> 00:05:04.789 a little bit at the end.
NOTE Confidence: 0.914410145454545

00:05:06.830 --> 00:05:09.049 So what are the causes of epilepsy
NOTE Confidence: 0.914410145454545

00:05:09.049 --> 00:05:10.470 where they're quite varied,
NOTE Confidence: 0.914410145454545

00:05:10.470 --> 00:05:12.426 They include things like brain injury,
NOTE Confidence: 0.914410145454545

00:05:12.430 --> 00:05:15.174 so trauma to the brain and lead
NOTE Confidence: 0.914410145454545

00:05:15.174 --> 00:05:18.298 to its stroke tumors and there's a
NOTE Confidence: 0.914410145454545

00:05:18.298 --> 00:05:20.733 variety of different genetic defects.
NOTE Confidence: 0.914410145454545

00:05:20.740 --> 00:05:22.456 But at least 50% of them,
NOTE Confidence: 0.914410145454545

00:05:22.460 --> 00:05:24.336 we really don't know the underlying cause,
NOTE Confidence: 0.914410145454545

00:05:24.340 --> 00:05:26.384 although it's believed that
NOTE Confidence: 0.914410145454545

00:05:26.384 --> 00:05:28.939 many of those are genetic.
NOTE Confidence: 0.914410145454545

00:05:28.940 --> 00:05:31.124 And that's really where this is
NOTE Confidence: 0.914410145454545

00:05:31.124 --> 00:05:33.954 led me to kind of start thinking
NOTE Confidence: 0.914410145454545

00:05:33.954 --> 00:05:36.540 about this and and this started
NOTE Confidence: 0.914410145454545

00:05:36.540 --> 00:05:39.004 a number of years ago when I got
NOTE Confidence: 0.914410145454545

00:05:39.004 --> 00:05:42.220 invited to give a talk at a.
NOTE Confidence: 0.914410145454545

00:05:42.220 --> 00:05:44.752 Early infantile epileptic encephalopathy,

NOTE Confidence: 0.914410145454545

00:05:44.752 --> 00:05:47.370 it's a type of syndrome that you

NOTE Confidence: 0.914410145454545

00:05:47.370 --> 00:05:49.176 see and at the time I, I,

NOTE Confidence: 0.914410145454545

00:05:49.176 --> 00:05:50.832 I started looking and I asked

NOTE Confidence: 0.914410145454545

00:05:50.832 --> 00:05:52.220 the question well how many,

NOTE Confidence: 0.914410145454545

00:05:52.220 --> 00:05:54.005 what do we know about the genes

NOTE Confidence: 0.914410145454545

00:05:54.005 --> 00:05:55.761 that are involved at that time And

NOTE Confidence: 0.914410145454545

00:05:55.761 --> 00:05:57.461 this list is much longer but this

NOTE Confidence: 0.914410145454545

00:05:57.461 --> 00:05:59.388 is where I started and and at the

NOTE Confidence: 0.914410145454545

00:05:59.388 --> 00:06:00.840 time there was just this relatively

NOTE Confidence: 0.914410145454545

00:06:00.889 --> 00:06:02.599 small number of genes that are

NOTE Confidence: 0.914410145454545

00:06:02.599 --> 00:06:03.986 involved there's there's now at

NOTE Confidence: 0.914410145454545

00:06:03.986 --> 00:06:06.455 least 152 genes involved in or

NOTE Confidence: 0.914410145454545

00:06:06.455 --> 00:06:08.972 associated with epilepsy and and I.

NOTE Confidence: 0.914410145454545

00:06:08.972 --> 00:06:11.276 I just started kind of thinking

NOTE Confidence: 0.914410145454545

00:06:11.276 --> 00:06:13.655 about this was kind of my own Geo,

NOTE Confidence: 0.914410145454545

00:06:13.660 --> 00:06:15.740 my own you know,
NOTE Confidence: 0.914410145454545

00:06:15.740 --> 00:06:19.844 kind of analysis and I was able to kind
NOTE Confidence: 0.914410145454545

00:06:19.844 --> 00:06:23.939 of orc or divide them up into nuclear genes,
NOTE Confidence: 0.914410145454545

00:06:23.940 --> 00:06:26.139 membrane associated genes.
NOTE Confidence: 0.914410145454545

00:06:26.139 --> 00:06:29.800 These are mostly receptors,
NOTE Confidence: 0.914410145454545

00:06:29.800 --> 00:06:32.880 transporters and channels,
NOTE Confidence: 0.914410145454545

00:06:32.880 --> 00:06:34.500 cytoplasmic proteins.
NOTE Confidence: 0.914410145454545

00:06:34.500 --> 00:06:36.930 And then interestingly,
NOTE Confidence: 0.914410145454545

00:06:36.930 --> 00:06:38.830 a number of mitochondrial
NOTE Confidence: 0.914410145454545

00:06:38.830 --> 00:06:40.730 disease genes came up.
NOTE Confidence: 0.914410145454545

00:06:40.730 --> 00:06:42.737 And So what I'm going to do today is
NOTE Confidence: 0.914410145454545

00:06:42.737 --> 00:06:44.945 take you through two of these because
NOTE Confidence: 0.914410145454545

00:06:44.945 --> 00:06:46.545 we've started studying the nuclear
NOTE Confidence: 0.914410145454545

00:06:46.545 --> 00:06:48.849 genes and I'm going to talk about a RX,
NOTE Confidence: 0.914410145454545

00:06:48.850 --> 00:06:50.752 the first one in that line,
NOTE Confidence: 0.914410145454545

00:06:50.752 --> 00:06:52.564 for quite a bit of time.

NOTE Confidence: 0.914410145454545
00:06:52.570 --> 00:06:54.089 And then I'm going to switch over
NOTE Confidence: 0.914410145454545
00:06:54.089 --> 00:06:55.924 and tell you a little bit about
NOTE Confidence: 0.914410145454545
00:06:55.924 --> 00:06:57.339 mitochondrial ones and how those
NOTE Confidence: 0.914410145454545
00:06:57.339 --> 00:06:58.996 actually came together in thinking
NOTE Confidence: 0.914410145454545
00:06:58.996 --> 00:07:00.408 about these different disorders.
NOTE Confidence: 0.936228169
00:07:02.450 --> 00:07:04.898 So just as a very brief primer to get
NOTE Confidence: 0.936228169
00:07:04.898 --> 00:07:07.978 started, just to remind everyone about the
NOTE Confidence: 0.936228169
00:07:07.978 --> 00:07:10.130 neocortex and for some of the audience,
NOTE Confidence: 0.936228169
00:07:10.130 --> 00:07:11.090 I'm sure this is review,
NOTE Confidence: 0.936228169
00:07:11.090 --> 00:07:13.650 but just to remind people,
NOTE Confidence: 0.936228169
00:07:13.650 --> 00:07:14.770 I think you can see my pointer,
NOTE Confidence: 0.936228169
00:07:14.770 --> 00:07:16.758 yeah, so layer one of the cortex
NOTE Confidence: 0.936228169
00:07:16.758 --> 00:07:18.968 is known as the molecular layer.
NOTE Confidence: 0.936228169
00:07:18.970 --> 00:07:20.400 This is in the mature
NOTE Confidence: 0.936228169
00:07:20.400 --> 00:07:21.378 brain during development.
NOTE Confidence: 0.936228169

00:07:21.378 --> 00:07:22.410 It's very important.
NOTE Confidence: 0.936228169

00:07:22.410 --> 00:07:24.475 It's also known as the marginal zone
NOTE Confidence: 0.936228169

00:07:24.475 --> 00:07:26.485 where there's a cell type called
NOTE Confidence: 0.936228169

00:07:26.485 --> 00:07:28.260 the Chorizius neuron which makes.
NOTE Confidence: 0.936228169

00:07:28.260 --> 00:07:30.042 Realin, which is important for the
NOTE Confidence: 0.936228169

00:07:30.042 --> 00:07:31.580 organization of the sixth layer,
NOTE Confidence: 0.936228169

00:07:31.580 --> 00:07:34.345 the laminar cortex layer two is known
NOTE Confidence: 0.936228169

00:07:34.345 --> 00:07:37.099 as the external granular cell layer.
NOTE Confidence: 0.936228169

00:07:37.100 --> 00:07:39.858 This is the mostly an input layer,
NOTE Confidence: 0.936228169

00:07:39.860 --> 00:07:44.308 a local input layer to the neocortex layer
NOTE Confidence: 0.936228169

00:07:44.308 --> 00:07:47.480 three is the external pyramidal cell layer.
NOTE Confidence: 0.936228169

00:07:47.480 --> 00:07:51.113 Now I want to take this moment to say
NOTE Confidence: 0.936228169

00:07:51.113 --> 00:07:53.738 that all layers have both excited to
NOTE Confidence: 0.936228169

00:07:53.740 --> 00:07:56.220 have pyramidal and granular neurons.
NOTE Confidence: 0.936228169

00:07:56.220 --> 00:07:58.326 It's just the relative distribution that
NOTE Confidence: 0.936228169

00:07:58.326 --> 00:08:00.966 give rise to it being an an external,

NOTE Confidence: 0.936228169

00:08:00.966 --> 00:08:02.964 I'm sorry, a granular layer versus

NOTE Confidence: 0.936228169

00:08:02.964 --> 00:08:04.536 a paramidal cell layer.

NOTE Confidence: 0.936228169

00:08:04.536 --> 00:08:07.888 So we have an external paramidal cell layer,

NOTE Confidence: 0.936228169

00:08:07.888 --> 00:08:08.824 layer 3.

NOTE Confidence: 0.936228169

00:08:08.824 --> 00:08:11.580 Then you have a internal granular

NOTE Confidence: 0.936228169

00:08:11.580 --> 00:08:14.220 cell layer which is layer 4.

NOTE Confidence: 0.936228169

00:08:14.220 --> 00:08:15.860 These layers actually define

NOTE Confidence: 0.936228169

00:08:15.860 --> 00:08:17.500 the different cortical regions.

NOTE Confidence: 0.936228169

00:08:17.500 --> 00:08:18.148 So for example,

NOTE Confidence: 0.936228169

00:08:18.148 --> 00:08:19.660 if you look in the visual cortex,

NOTE Confidence: 0.936228169

00:08:19.660 --> 00:08:21.180 this is from motor cortex,

NOTE Confidence: 0.936228169

00:08:21.180 --> 00:08:23.140 if you look at the visual cortex.

NOTE Confidence: 0.936228169

00:08:23.140 --> 00:08:25.390 Layer 4 is dramatically expanded and

NOTE Confidence: 0.936228169

00:08:25.390 --> 00:08:28.138 it's the major input from the thalamus,

NOTE Confidence: 0.936228169

00:08:28.140 --> 00:08:30.744 whereas in the motor cortex there's

NOTE Confidence: 0.936228169

00:08:30.744 --> 00:08:33.099 almost no layer four at all.
NOTE Confidence: 0.936228169

00:08:33.100 --> 00:08:34.744 In contrast, layer 5,
NOTE Confidence: 0.936228169

00:08:34.744 --> 00:08:36.660 which is your primary
NOTE Confidence: 0.9244197933333333

00:08:39.220 --> 00:08:40.952 output pyramidal cell layer,
NOTE Confidence: 0.9244197933333333

00:08:40.952 --> 00:08:42.280 that goes, for example,
NOTE Confidence: 0.9244197933333333

00:08:42.280 --> 00:08:43.660 the large bed cells that go
NOTE Confidence: 0.9244197933333333

00:08:43.660 --> 00:08:44.940 down in the spinal cord,
NOTE Confidence: 0.9244197933333333

00:08:44.940 --> 00:08:47.220 those are all in layer 5.
NOTE Confidence: 0.9244197933333333

00:08:47.220 --> 00:08:48.860 Those project to other parts of the brain,
NOTE Confidence: 0.9244197933333333

00:08:48.860 --> 00:08:50.210 including to the other side
NOTE Confidence: 0.9244197933333333

00:08:50.210 --> 00:08:52.744 of the brain and then layer 6.
NOTE Confidence: 0.9244197933333333

00:08:52.744 --> 00:08:55.330 Which is against the white matter.
NOTE Confidence: 0.9244197933333333

00:08:55.330 --> 00:08:57.738 This is the what's known as the multiform
NOTE Confidence: 0.9244197933333333

00:08:57.738 --> 00:08:59.673 or fusiform layer and it consists
NOTE Confidence: 0.9244197933333333

00:08:59.673 --> 00:09:01.581 of a variety of different neuronal
NOTE Confidence: 0.9244197933333333

00:09:01.643 --> 00:09:03.687 types and has both input and output.

NOTE Confidence: 0.9244197933333333
00:09:03.690 --> 00:09:06.050 And then below that is the white matter.
NOTE Confidence: 0.9244197933333333
00:09:06.050 --> 00:09:08.490 So that's the six layers of the cortex.
NOTE Confidence: 0.9244197933333333
00:09:08.490 --> 00:09:11.010 And these layers are composed,
NOTE Confidence: 0.9244197933333333
00:09:11.010 --> 00:09:13.650 as I said of of these granular neurons,
NOTE Confidence: 0.9244197933333333
00:09:13.650 --> 00:09:17.094 here labeled non spining neurons and the
NOTE Confidence: 0.9244197933333333
00:09:17.094 --> 00:09:20.724 spining neurons or the pyramidal cells now.
NOTE Confidence: 0.9244197933333333
00:09:20.724 --> 00:09:23.568 These two cell types compose the
NOTE Confidence: 0.9244197933333333
00:09:23.570 --> 00:09:25.845 major 2 cell types in the cortex,
NOTE Confidence: 0.9244197933333333
00:09:25.850 --> 00:09:26.960 the excitatory neurons,
NOTE Confidence: 0.9244197933333333
00:09:26.960 --> 00:09:28.810 those are the spiny ones,
NOTE Confidence: 0.9244197933333333
00:09:28.810 --> 00:09:31.090 they use glutamate as a neurotransmitter,
NOTE Confidence: 0.9244197933333333
00:09:31.090 --> 00:09:34.548 and the non spiny or the inhibitory
NOTE Confidence: 0.9244197933333333
00:09:34.548 --> 00:09:36.890 interneurons which all use GABA.
NOTE Confidence: 0.9244197933333333
00:09:36.890 --> 00:09:37.928 But as you can see here,
NOTE Confidence: 0.9244197933333333
00:09:37.930 --> 00:09:39.315 there's actually many different forms
NOTE Confidence: 0.9244197933333333

00:09:39.315 --> 00:09:41.090 of each of these different neurons,
NOTE Confidence: 0.9244197933333333

00:09:41.090 --> 00:09:41.732 and there's.
NOTE Confidence: 0.9244197933333333

00:09:41.732 --> 00:09:44.300 Probably on the order of 30 to 40
NOTE Confidence: 0.9244197933333333

00:09:44.371 --> 00:09:46.465 or more of the excitatory neurons
NOTE Confidence: 0.9244197933333333

00:09:46.465 --> 00:09:49.407 and in the order of 60 of different
NOTE Confidence: 0.9244197933333333

00:09:49.407 --> 00:09:51.252 types of inhibitory neurons or
NOTE Confidence: 0.9244197933333333

00:09:51.252 --> 00:09:55.350 the these non spiny interneurons.
NOTE Confidence: 0.9244197933333333

00:09:55.350 --> 00:09:58.994 Normal cortical development requires
NOTE Confidence: 0.9244197933333333

00:09:58.994 --> 00:10:03.338 an integration of both of these
NOTE Confidence: 0.9244197933333333

00:10:03.338 --> 00:10:05.510 types of neurons.
NOTE Confidence: 0.9244197933333333

00:10:05.510 --> 00:10:07.568 If you don't have the excitatory
NOTE Confidence: 0.9244197933333333

00:10:07.568 --> 00:10:09.785 neurons and the inhibitory neurons you
NOTE Confidence: 0.9244197933333333

00:10:09.785 --> 00:10:11.740 get disruptions in normal cortical.
NOTE Confidence: 0.9244197933333333

00:10:11.740 --> 00:10:12.282 Functions,
NOTE Confidence: 0.9244197933333333

00:10:12.282 --> 00:10:14.992 circuits that result in functional
NOTE Confidence: 0.9244197933333333

00:10:14.992 --> 00:10:18.048 defects and those give rise to a

NOTE Confidence: 0.9244197933333333
00:10:18.048 --> 00:10:20.500 variety of different developmental disorders.
NOTE Confidence: 0.9244197933333333
00:10:20.500 --> 00:10:22.756 And what you can see here is the
NOTE Confidence: 0.9244197933333333
00:10:22.756 --> 00:10:24.624 different types of excitatory and
NOTE Confidence: 0.9244197933333333
00:10:24.624 --> 00:10:27.096 inhibitory neurons connect in different ways.
NOTE Confidence: 0.9244197933333333
00:10:27.100 --> 00:10:29.062 So there are some inhibitory neurons
NOTE Confidence: 0.9244197933333333
00:10:29.062 --> 00:10:31.304 like this green one that predominantly
NOTE Confidence: 0.9244197933333333
00:10:31.304 --> 00:10:34.325 function by connecting on the Axon and
NOTE Confidence: 0.9244197933333333
00:10:34.325 --> 00:10:37.379 the proximal Axon and the cell body,
NOTE Confidence: 0.9244197933333333
00:10:37.380 --> 00:10:39.230 whereas others are going to
NOTE Confidence: 0.9244197933333333
00:10:39.230 --> 00:10:40.710 connect more on dendrites.
NOTE Confidence: 0.9244197933333333
00:10:40.710 --> 00:10:43.310 And some just on the cell body itself,
NOTE Confidence: 0.9244197933333333
00:10:43.310 --> 00:10:45.042 like this purple one.
NOTE Confidence: 0.9244197933333333
00:10:45.042 --> 00:10:48.364 And these are all required to appropriately
NOTE Confidence: 0.9244197933333333
00:10:48.364 --> 00:10:51.549 modulate circuits in the brain.
NOTE Confidence: 0.9244197933333333
00:10:51.550 --> 00:10:53.692 So you need all these different types
NOTE Confidence: 0.9244197933333333

00:10:53.692 --> 00:10:55.635 to get the appropriate development
NOTE Confidence: 0.9244197933333333

00:10:55.635 --> 00:10:58.503 and function of the cerebral cortex.
NOTE Confidence: 0.9171913833333333

00:11:01.590 --> 00:11:04.020 Well, what's interesting also about this
NOTE Confidence: 0.9171913833333333

00:11:04.020 --> 00:11:07.338 is that these two different neuronal types
NOTE Confidence: 0.9171913833333333

00:11:07.338 --> 00:11:10.043 come from different progenitor zones.
NOTE Confidence: 0.9171913833333333

00:11:10.050 --> 00:11:14.210 Now in the for the cortical excitatory
NOTE Confidence: 0.9171913833333333

00:11:14.210 --> 00:11:16.302 neurons, they are essentially
NOTE Confidence: 0.9171913833333333

00:11:16.302 --> 00:11:18.486 all driven from or derived from
NOTE Confidence: 0.9171913833333333

00:11:18.486 --> 00:11:20.610 the cortical ventricular zone,
NOTE Confidence: 0.9171913833333333

00:11:20.610 --> 00:11:23.352 that dorsal portion of progenitor cells
NOTE Confidence: 0.9171913833333333

00:11:23.352 --> 00:11:26.790 that are along the ventricle and these
NOTE Confidence: 0.9171913833333333

00:11:26.790 --> 00:11:29.250 cells divide and they migrate out.
NOTE Confidence: 0.9171913833333333

00:11:29.250 --> 00:11:31.329 This a lot of this work fundamentally
NOTE Confidence: 0.9171913833333333

00:11:31.329 --> 00:11:33.202 done by Doctor Rakesh who's sitting
NOTE Confidence: 0.9171913833333333

00:11:33.202 --> 00:11:34.737 here in the front row.
NOTE Confidence: 0.9171913833333333

00:11:34.740 --> 00:11:37.220 Has shown that these cells migrate out the

NOTE Confidence: 0.9171913833333333

00:11:37.220 --> 00:11:39.655 first form of what's called a preplate A,

NOTE Confidence: 0.9171913833333333

00:11:39.660 --> 00:11:40.832 the call ritzius neuron,

NOTE Confidence: 0.9171913833333333

00:11:40.832 --> 00:11:42.297 and then a subplate neuron,

NOTE Confidence: 0.9171913833333333

00:11:42.300 --> 00:11:45.420 which is really important for the

NOTE Confidence: 0.9171913833333333

00:11:45.420 --> 00:11:48.284 ultimate connection between the thalamic

NOTE Confidence: 0.9171913833333333

00:11:48.284 --> 00:11:51.214 nuclei and the cortical region.

NOTE Confidence: 0.9171913833333333

00:11:51.220 --> 00:11:52.480 So defining, for example,

NOTE Confidence: 0.9171913833333333

00:11:52.480 --> 00:11:54.370 the visual cortex in the lateral

NOTE Confidence: 0.9171913833333333

00:11:54.430 --> 00:11:55.300 geniculate body.

NOTE Confidence: 0.9171913833333333

00:11:55.300 --> 00:11:56.818 For those connections to be made,

NOTE Confidence: 0.9171913833333333

00:11:56.820 --> 00:11:59.380 it requires those subplate neurons.

NOTE Confidence: 0.9171913833333333

00:11:59.380 --> 00:12:01.718 They that the call ritzius neuron and

NOTE Confidence: 0.9171913833333333

00:12:01.718 --> 00:12:03.610 the subplate neuron are important.

NOTE Confidence: 0.9171913833333333

00:12:03.610 --> 00:12:06.410 We're also separating and the

NOTE Confidence: 0.9171913833333333

00:12:06.410 --> 00:12:07.530 definitive cortex,

NOTE Confidence: 0.9171913833333333

00:12:07.530 --> 00:12:10.050 that layer 2 through 6.
NOTE Confidence: 0.9171913833333333

00:12:10.050 --> 00:12:12.276 Fill in between those and they fill
NOTE Confidence: 0.9171913833333333

00:12:12.276 --> 00:12:15.078 in in an inverse pattern from the
NOTE Confidence: 0.9171913833333333

00:12:15.078 --> 00:12:17.730 deep layer to the superficial layer.
NOTE Confidence: 0.9171913833333333

00:12:17.730 --> 00:12:18.660 In mice,
NOTE Confidence: 0.9171913833333333

00:12:18.660 --> 00:12:20.985 all of the excitatory neurons
NOTE Confidence: 0.9171913833333333

00:12:20.985 --> 00:12:23.090 come from this region,
NOTE Confidence: 0.9171913833333333

00:12:23.090 --> 00:12:25.407 and it looks like in humans too,
NOTE Confidence: 0.9171913833333333

00:12:25.410 --> 00:12:25.998 inhibitory neurons,
NOTE Confidence: 0.9171913833333333

00:12:25.998 --> 00:12:28.350 which I'll show you on the next slide.
NOTE Confidence: 0.9171913833333333

00:12:28.350 --> 00:12:30.401 There may be some that are derived
NOTE Confidence: 0.9171913833333333

00:12:30.401 --> 00:12:32.205 from the ventricular zone in
NOTE Confidence: 0.9171913833333333

00:12:32.205 --> 00:12:34.404 the in the human dorsal cortex,
NOTE Confidence: 0.9171913833333333

00:12:34.404 --> 00:12:37.389 but it does not appear to be in the mouse.
NOTE Confidence: 0.9171913833333333

00:12:37.390 --> 00:12:40.267 In the human and in the mouse,
NOTE Confidence: 0.9171913833333333

00:12:40.270 --> 00:12:41.884 the vast majority are from another

NOTE Confidence: 0.9171913833333333

00:12:41.884 --> 00:12:43.629 progenitor region and I'll show you that.

NOTE Confidence: 0.9171913833333333

00:12:43.630 --> 00:12:45.830 Next I do want to just briefly mention,

NOTE Confidence: 0.9171913833333333

00:12:45.830 --> 00:12:47.104 because I'm going to talk about it,

NOTE Confidence: 0.9171913833333333

00:12:47.110 --> 00:12:48.870 there's an intermediate progenitor zone.

NOTE Confidence: 0.9171913833333333

00:12:48.870 --> 00:12:51.030 This is called the sub ventricular

NOTE Confidence: 0.9171913833333333

00:12:51.030 --> 00:12:53.910 zone and this is where cells.

NOTE Confidence: 0.9171913833333333

00:12:53.910 --> 00:12:55.970 Actually go from the ventricular

NOTE Confidence: 0.9171913833333333

00:12:55.970 --> 00:12:58.630 zone being a stem cell to this

NOTE Confidence: 0.9171913833333333

00:12:58.630 --> 00:13:01.205 this subventricular zone where they

NOTE Confidence: 0.9171913833333333

00:13:01.205 --> 00:13:03.265 form an intermediate progenitor.

NOTE Confidence: 0.9171913833333333

00:13:03.270 --> 00:13:05.820 Go through one or several divisions

NOTE Confidence: 0.9171913833333333

00:13:05.820 --> 00:13:07.682 before ultimately and exiting the cell

NOTE Confidence: 0.9171913833333333

00:13:07.682 --> 00:13:09.630 cycle and going up into the cortex.

NOTE Confidence: 0.905435112

00:13:13.030 --> 00:13:16.350 Now this, this is the what I was showing you.

NOTE Confidence: 0.905435112

00:13:16.350 --> 00:13:18.667 Here's the this is a hemi section.

NOTE Confidence: 0.905435112

00:13:18.670 --> 00:13:20.650 Imagine this being a hemi
NOTE Confidence: 0.905435112

00:13:20.650 --> 00:13:22.234 section through the brain.
NOTE Confidence: 0.905435112

00:13:22.240 --> 00:13:24.354 And it could be any mammalian species.
NOTE Confidence: 0.905435112

00:13:24.360 --> 00:13:26.152 And it's one side.
NOTE Confidence: 0.905435112

00:13:26.152 --> 00:13:28.392 So this is the midline,
NOTE Confidence: 0.905435112

00:13:28.400 --> 00:13:31.438 this is dorsal or the top, this is ventral,
NOTE Confidence: 0.905435112

00:13:31.438 --> 00:13:33.274 the bottom and this is lateral.
NOTE Confidence: 0.905435112

00:13:33.280 --> 00:13:34.184 The cortical ventricular zone
NOTE Confidence: 0.905435112

00:13:34.184 --> 00:13:35.314 that I've been talking about,
NOTE Confidence: 0.905435112

00:13:35.320 --> 00:13:36.490 where the excitatory
NOTE Confidence: 0.905435112

00:13:36.490 --> 00:13:38.440 neurons come from is here.
NOTE Confidence: 0.905435112

00:13:38.440 --> 00:13:40.135 And then there's this structure
NOTE Confidence: 0.905435112

00:13:40.135 --> 00:13:41.830 known as the ganglionic eminence
NOTE Confidence: 0.905435112

00:13:41.889 --> 00:13:43.639 in the ventral part of the brain.
NOTE Confidence: 0.905435112

00:13:43.640 --> 00:13:45.105 This is where these inhibitory
NOTE Confidence: 0.905435112

00:13:45.105 --> 00:13:46.277 neurons are derived from.

NOTE Confidence: 0.905435112

00:13:46.280 --> 00:13:49.936 And what's interesting is that if you look.

NOTE Confidence: 0.905435112

00:13:49.940 --> 00:13:50.888 Along the dorsal,

NOTE Confidence: 0.905435112

00:13:50.888 --> 00:13:53.504 ventral axis from the neural at the beginning

NOTE Confidence: 0.905435112

00:13:53.504 --> 00:13:56.256 of the nervous system in this neural tube,

NOTE Confidence: 0.905435112

00:13:56.260 --> 00:13:57.892 from dorsal to ventral,

NOTE Confidence: 0.905435112

00:13:57.892 --> 00:14:00.636 you get different neural types defined

NOTE Confidence: 0.905435112

00:14:00.636 --> 00:14:03.420 by different genetic pathways.

NOTE Confidence: 0.905435112

00:14:03.420 --> 00:14:05.820 And you see that also in the forebrain.

NOTE Confidence: 0.905435112

00:14:05.820 --> 00:14:07.136 So this is in the spinal cord,

NOTE Confidence: 0.905435112

00:14:07.140 --> 00:14:08.148 but in the forebrain.

NOTE Confidence: 0.905435112

00:14:08.148 --> 00:14:09.660 And there's specific genes that are

NOTE Confidence: 0.905435112

00:14:09.712 --> 00:14:11.042 expressed in these different regions

NOTE Confidence: 0.905435112

00:14:11.042 --> 00:14:12.763 that give rise to these different

NOTE Confidence: 0.905435112

00:14:12.763 --> 00:14:14.498 progenitors and different cell types.

NOTE Confidence: 0.905435112

00:14:14.500 --> 00:14:14.844 And again,

NOTE Confidence: 0.905435112

00:14:14.844 --> 00:14:15.876 I'm going to come back to
NOTE Confidence: 0.905435112

00:14:15.876 --> 00:14:16.740 talk about that as well.
NOTE Confidence: 0.935781098888889

00:14:19.180 --> 00:14:21.016 So what does this look like in the human?
NOTE Confidence: 0.935781098888889

00:14:21.020 --> 00:14:22.740 So on your left side,
NOTE Confidence: 0.935781098888889

00:14:22.740 --> 00:14:27.380 that's a human about 7 1/2 weeks gestation.
NOTE Confidence: 0.935781098888889

00:14:27.380 --> 00:14:30.076 And you can see the ganglionic eminence where
NOTE Confidence: 0.935781098888889

00:14:30.076 --> 00:14:32.012 these inhibitory neurons are predominately
NOTE Confidence: 0.935781098888889

00:14:32.012 --> 00:14:34.017 coming from the ventricular zone.
NOTE Confidence: 0.935781098888889

00:14:34.020 --> 00:14:36.334 And this here is the preplate and
NOTE Confidence: 0.935781098888889

00:14:36.334 --> 00:14:37.738 you can see the preplate forming,
NOTE Confidence: 0.935781098888889

00:14:37.740 --> 00:14:39.072 it's a little larger,
NOTE Confidence: 0.935781098888889

00:14:39.072 --> 00:14:41.540 It actually starts in the ventrolateral
NOTE Confidence: 0.935781098888889

00:14:41.540 --> 00:14:45.292 location and it moves. Moves up,
NOTE Confidence: 0.935781098888889

00:14:45.292 --> 00:14:47.860 so it doesn't all develop at the same time.
NOTE Confidence: 0.935781098888889

00:14:47.860 --> 00:14:50.338 It also goes from anterior to posterior,
NOTE Confidence: 0.935781098888889

00:14:50.340 --> 00:14:51.828 so you can see that in

NOTE Confidence: 0.935781098888889
00:14:51.828 --> 00:14:52.820 the very dorsal regions,
NOTE Confidence: 0.935781098888889
00:14:52.820 --> 00:14:54.296 there's not even a preplate yet.
NOTE Confidence: 0.935781098888889
00:14:54.300 --> 00:14:59.539 At 7 1/2 weeks by 20 weeks,
NOTE Confidence: 0.935781098888889
00:14:59.540 --> 00:15:01.380 the station which is here,
NOTE Confidence: 0.935781098888889
00:15:01.380 --> 00:15:02.540 you can see the hippocampus.
NOTE Confidence: 0.935781098888889
00:15:02.540 --> 00:15:04.220 So we're looking at the temporal lobe,
NOTE Confidence: 0.935781098888889
00:15:04.220 --> 00:15:07.140 and essentially all the neurons,
NOTE Confidence: 0.935781098888889
00:15:07.140 --> 00:15:08.640 with a few exceptions,
NOTE Confidence: 0.935781098888889
00:15:08.640 --> 00:15:10.515 are already in the cortex.
NOTE Confidence: 0.935781098888889
00:15:10.520 --> 00:15:11.820 So they've migrated out,
NOTE Confidence: 0.935781098888889
00:15:11.820 --> 00:15:13.520 but they haven't yet differentiated
NOTE Confidence: 0.935781098888889
00:15:13.520 --> 00:15:15.120 and defined themselves in
NOTE Confidence: 0.935781098888889
00:15:15.120 --> 00:15:16.320 different laminar organization,
NOTE Confidence: 0.935781098888889
00:15:16.320 --> 00:15:17.260 but they are molecularly
NOTE Confidence: 0.935781098888889
00:15:17.260 --> 00:15:18.200 defined by that time.
NOTE Confidence: 0.935781098888889

00:15:18.200 --> 00:15:18.804 All right.
NOTE Confidence: 0.935781098888889

00:15:18.804 --> 00:15:21.320 So that's a little bit of a kind
NOTE Confidence: 0.935781098888889

00:15:21.320 --> 00:15:23.720 of just background to get you
NOTE Confidence: 0.935781098888889

00:15:23.720 --> 00:15:25.224 to thinking about the studies
NOTE Confidence: 0.935781098888889

00:15:25.224 --> 00:15:26.880 I'm going to tell you about.
NOTE Confidence: 0.935781098888889

00:15:26.880 --> 00:15:29.064 I'm going to start out telling you
NOTE Confidence: 0.935781098888889

00:15:29.064 --> 00:15:30.370 about that transcription factor
NOTE Confidence: 0.935781098888889

00:15:30.370 --> 00:15:31.984 that is associated with epilepsy.
NOTE Confidence: 0.935781098888889

00:15:31.984 --> 00:15:33.360 It's actually associated with
NOTE Confidence: 0.935781098888889

00:15:33.360 --> 00:15:35.520 structural defects of the brain as well.
NOTE Confidence: 0.935781098888889

00:15:35.520 --> 00:15:36.822 It's called ARX.
NOTE Confidence: 0.935781098888889

00:15:36.822 --> 00:15:38.558 Aristoleless related homeobox gene,
NOTE Confidence: 0.935781098888889

00:15:38.560 --> 00:15:41.530 so it's related to the Drosophila
NOTE Confidence: 0.935781098888889

00:15:41.530 --> 00:15:44.595 ristolis gene and this gene is on
NOTE Confidence: 0.935781098888889

00:15:44.595 --> 00:15:47.564 the X chromosome and in males what
NOTE Confidence: 0.935781098888889

00:15:47.564 --> 00:15:51.652 you see is a spectrum of neurologic

NOTE Confidence: 0.935781098888889
00:15:51.652 --> 00:15:53.712 and cognitive deficits and and
NOTE Confidence: 0.935781098888889
00:15:53.712 --> 00:15:56.709 and I really was attracted to this
NOTE Confidence: 0.935781098888889
00:15:56.709 --> 00:15:58.839 gene because of this spectrum.
NOTE Confidence: 0.935781098888889
00:15:58.840 --> 00:16:01.400 So some mutations resulted in
NOTE Confidence: 0.935781098888889
00:16:01.400 --> 00:16:04.770 hydrocephalus and and abnormal genitalia.
NOTE Confidence: 0.935781098888889
00:16:04.770 --> 00:16:05.770 That's a pretty rare one.
NOTE Confidence: 0.935781098888889
00:16:05.770 --> 00:16:07.156 What's most common was the second
NOTE Confidence: 0.935781098888889
00:16:07.156 --> 00:16:09.770 one on there, something called X lag,
NOTE Confidence: 0.935781098888889
00:16:09.770 --> 00:16:12.650 X link lizencephaly with ambiguous genitalia.
NOTE Confidence: 0.935781098888889
00:16:12.650 --> 00:16:14.246 But you could also have a genesis,
NOTE Confidence: 0.935781098888889
00:16:14.250 --> 00:16:15.720 the corpus callosum.
NOTE Confidence: 0.935781098888889
00:16:15.720 --> 00:16:18.170 You could have infantile spasms.
NOTE Confidence: 0.935781098888889
00:16:18.170 --> 00:16:19.654 That was what I showed you in
NOTE Confidence: 0.935781098888889
00:16:19.654 --> 00:16:20.290 that child earlier.
NOTE Confidence: 0.935781098888889
00:16:20.290 --> 00:16:22.570 That does have an ARX mutation
NOTE Confidence: 0.935781098888889

00:16:22.570 --> 00:16:23.848 and a variety of other things,
NOTE Confidence: 0.935781098888889

00:16:23.850 --> 00:16:26.330 down to intellectual disabilities
NOTE Confidence: 0.935781098888889

00:16:26.330 --> 00:16:27.570 with seizures.
NOTE Confidence: 0.93622824

00:16:29.890 --> 00:16:31.522 What I want to point out is that
NOTE Confidence: 0.93622824

00:16:31.522 --> 00:16:33.379 at the top of this list are
NOTE Confidence: 0.93622824

00:16:33.379 --> 00:16:34.769 structural defects of the brain,
NOTE Confidence: 0.93622824

00:16:34.770 --> 00:16:37.780 lizencephaly and a genus of the corpus
NOTE Confidence: 0.93622824

00:16:37.780 --> 00:16:40.562 callosum, and they have epilepsy
NOTE Confidence: 0.93622824

00:16:40.562 --> 00:16:42.326 and intellectual disabilities.
NOTE Confidence: 0.93622824

00:16:42.330 --> 00:16:44.570 At the bottom of the list are brains
NOTE Confidence: 0.93622824

00:16:44.570 --> 00:16:47.938 that are structurally normal but
NOTE Confidence: 0.93622824

00:16:47.938 --> 00:16:49.978 have the exact same intellectual
NOTE Confidence: 0.93622824

00:16:49.978 --> 00:16:51.202 disabilities and epilepsy,
NOTE Confidence: 0.93622824

00:16:51.210 --> 00:16:54.045 presenting at almost the exact same time.
NOTE Confidence: 0.93622824

00:16:54.050 --> 00:16:55.324 And this was really curious to me.
NOTE Confidence: 0.93622824

00:16:55.330 --> 00:16:58.018 How can you have these two different?

NOTE Confidence: 0.93622824

00:16:58.020 --> 00:16:58.875 Kind of phenotypes,

NOTE Confidence: 0.93622824

00:16:58.875 --> 00:17:00.300 one with a structurally abnormal

NOTE Confidence: 0.93622824

00:17:00.300 --> 00:17:02.017 brain and one with a normal brain,

NOTE Confidence: 0.93622824

00:17:02.020 --> 00:17:05.380 what's structurally normal based on MRI

NOTE Confidence: 0.93622824

00:17:05.380 --> 00:17:09.778 and have the same neurologic presentation.

NOTE Confidence: 0.93622824

00:17:09.780 --> 00:17:11.684 And I want to try and address that

NOTE Confidence: 0.93622824

00:17:11.684 --> 00:17:13.848 and I hope by the end of today I

NOTE Confidence: 0.93622824

00:17:13.848 --> 00:17:15.977 will be able to have addressed that.

NOTE Confidence: 0.93622824

00:17:15.980 --> 00:17:17.708 I will say that females were

NOTE Confidence: 0.93622824

00:17:17.708 --> 00:17:19.979 thought to have a genesis of the

NOTE Confidence: 0.93622824

00:17:19.979 --> 00:17:21.739 corpus callosum in some cases,

NOTE Confidence: 0.93622824

00:17:21.740 --> 00:17:23.188 otherwise they were normal.

NOTE Confidence: 0.93622824

00:17:23.188 --> 00:17:24.998 We have shown in publications

NOTE Confidence: 0.93622824

00:17:24.998 --> 00:17:26.880 that that's actually not true.

NOTE Confidence: 0.93622824

00:17:26.880 --> 00:17:28.320 I'm not going to talk about females today,

NOTE Confidence: 0.93622824

00:17:28.320 --> 00:17:31.122 but I'm happy to talk if you want to at the
NOTE Confidence: 0.93622824

00:17:31.122 --> 00:17:33.754 end about the genetics and how that happens.
NOTE Confidence: 0.93622824

00:17:33.760 --> 00:17:34.960 So let's talk about a RX.
NOTE Confidence: 0.93622824

00:17:34.960 --> 00:17:37.636 It's a, it's got 5 exons.
NOTE Confidence: 0.93622824

00:17:37.640 --> 00:17:38.912 The first, sorry,
NOTE Confidence: 0.93622824

00:17:38.912 --> 00:17:41.880 the 2nd exon at the very end.
NOTE Confidence: 0.93622824

00:17:41.880 --> 00:17:42.908 The second exon's the
NOTE Confidence: 0.93622824

00:17:42.908 --> 00:17:44.193 largest at the very end.
NOTE Confidence: 0.93622824

00:17:44.200 --> 00:17:47.040 It has the beginning of its paired like
NOTE Confidence: 0.93622824

00:17:47.040 --> 00:17:48.657 transcription homeo domain component.
NOTE Confidence: 0.93622824

00:17:48.657 --> 00:17:52.210 So it's got a paired like homeo domain.
NOTE Confidence: 0.93622824

00:17:52.210 --> 00:17:53.645 It's at the end of the second,
NOTE Confidence: 0.93622824

00:17:53.650 --> 00:17:55.702 going through the 3rd and into
NOTE Confidence: 0.93622824

00:17:55.702 --> 00:17:57.809 the beginning of the 4th exons,
NOTE Confidence: 0.93622824

00:17:57.810 --> 00:17:59.610 but I also and and and.
NOTE Confidence: 0.93622824

00:17:59.610 --> 00:18:01.535 So mutations at the top of that

NOTE Confidence: 0.93622824
00:18:01.535 --> 00:18:03.528 which are frame shift or deletions,
NOTE Confidence: 0.93622824
00:18:03.530 --> 00:18:05.430 give you that very severe
NOTE Confidence: 0.93622824
00:18:05.430 --> 00:18:07.330 structural defect of the brain,
NOTE Confidence: 0.93622824
00:18:07.330 --> 00:18:10.658 including the lizencephaly and
NOTE Confidence: 0.93622824
00:18:10.658 --> 00:18:13.890 the agents of the corpus callosum.
NOTE Confidence: 0.93622824
00:18:13.890 --> 00:18:16.795 But at the bottom, I'm not sure.
NOTE Confidence: 0.93622824
00:18:16.800 --> 00:18:19.040 Why the lettering didn't come out right,
NOTE Confidence: 0.93622824
00:18:19.040 --> 00:18:22.491 but it's at the bottom are some
NOTE Confidence: 0.93622824
00:18:22.491 --> 00:18:24.592 interesting mutations that are
NOTE Confidence: 0.93622824
00:18:24.592 --> 00:18:27.262 point mutations in very highly
NOTE Confidence: 0.93622824
00:18:27.262 --> 00:18:30.140 conserved amino acids and also
NOTE Confidence: 0.93622824
00:18:30.140 --> 00:18:32.480 these alanine tract expansion.
NOTE Confidence: 0.93622824
00:18:32.480 --> 00:18:35.600 So ARX has four alanine tracts in it.
NOTE Confidence: 0.949198762222222
00:18:38.120 --> 00:18:39.275 We really don't know much
NOTE Confidence: 0.949198762222222
00:18:39.275 --> 00:18:40.199 about these alanine tracts,
NOTE Confidence: 0.949198762222222

00:18:40.200 --> 00:18:42.795 but we now know that there's about 450
NOTE Confidence: 0.9491987622222222

00:18:42.795 --> 00:18:44.925 annotated genes in the human genome
NOTE Confidence: 0.9491987622222222

00:18:44.925 --> 00:18:47.558 that have an alanine tract in them.
NOTE Confidence: 0.9491987622222222

00:18:47.560 --> 00:18:49.360 75% of those are transcription factors.
NOTE Confidence: 0.9491987622222222

00:18:49.360 --> 00:18:51.352 So we think that it has something to
NOTE Confidence: 0.9491987622222222

00:18:51.352 --> 00:18:53.440 do with transcriptional regulation.
NOTE Confidence: 0.9491987622222222

00:18:53.440 --> 00:18:58.515 And there's now 9 or 10 genes that
NOTE Confidence: 0.9491987622222222

00:18:58.515 --> 00:19:01.400 have an alanine tract expansion
NOTE Confidence: 0.9491987622222222

00:19:01.400 --> 00:19:04.528 like you see in glutamine tract
NOTE Confidence: 0.9491987622222222

00:19:04.528 --> 00:19:06.320 expansions like Huntington's disease,
NOTE Confidence: 0.9491987622222222

00:19:06.320 --> 00:19:09.519 Kennedy syndrome, some of the HS P's,
NOTE Confidence: 0.9438383044444445

00:19:11.600 --> 00:19:13.765 those expansions in alanine tracts
NOTE Confidence: 0.9438383044444445

00:19:13.765 --> 00:19:15.497 though are relatively small.
NOTE Confidence: 0.9438383044444445

00:19:15.500 --> 00:19:18.140 On the order of three to
NOTE Confidence: 0.9438383044444445

00:19:18.140 --> 00:19:19.460 10 additional alanines.
NOTE Confidence: 0.9438383044444445

00:19:19.460 --> 00:19:21.692 And unlike the Huntington's disease and

NOTE Confidence: 0.943838304444445
00:19:21.692 --> 00:19:24.636 some of the others that show anticipation
NOTE Confidence: 0.943838304444445
00:19:24.636 --> 00:19:27.414 with very long glutamine tract expansions,
NOTE Confidence: 0.943838304444445
00:19:27.420 --> 00:19:30.885 these are very short and they're all
NOTE Confidence: 0.943838304444445
00:19:30.885 --> 00:19:33.951 developmental, they're not neurodegenerative,
NOTE Confidence: 0.943838304444445
00:19:33.951 --> 00:19:37.379 these are neurodevelopmental disorders.
NOTE Confidence: 0.943838304444445
00:19:37.380 --> 00:19:39.802 So we were quite curious about them
NOTE Confidence: 0.943838304444445
00:19:39.802 --> 00:19:43.020 because these give rise to the the same.
NOTE Confidence: 0.943838304444445
00:19:43.020 --> 00:19:45.180 Intellectual disabilities and epilepsy,
NOTE Confidence: 0.943838304444445
00:19:45.180 --> 00:19:47.830 but structurally normal brains and
NOTE Confidence: 0.943838304444445
00:19:47.830 --> 00:19:51.260 I'll be telling you about that today.
NOTE Confidence: 0.943838304444445
00:19:51.260 --> 00:19:53.696 So where is a RX expressed?
NOTE Confidence: 0.943838304444445
00:19:53.700 --> 00:19:57.161 Well, work from John Rubenstein's lab out
NOTE Confidence: 0.943838304444445
00:19:57.161 --> 00:19:58.988 in San Francisco showed that it's expressed
NOTE Confidence: 0.943838304444445
00:19:58.988 --> 00:20:00.820 early on in the ganglionic eminence.
NOTE Confidence: 0.943838304444445
00:20:00.820 --> 00:20:03.578 Here you can see by insight to
NOTE Confidence: 0.943838304444445

00:20:03.578 --> 00:20:05.499 hybridization and throughout the cortex
NOTE Confidence: 0.943838304444445

00:20:05.500 --> 00:20:08.013 and here we did an immunohistic chemistry
NOTE Confidence: 0.943838304444445

00:20:08.013 --> 00:20:10.268 with an antibody that we developed.
NOTE Confidence: 0.943838304444445

00:20:10.270 --> 00:20:11.894 And you can see that it's expressed
NOTE Confidence: 0.943838304444445

00:20:11.894 --> 00:20:13.510 strongly in the ganglionic eminence as
NOTE Confidence: 0.943838304444445

00:20:13.510 --> 00:20:15.547 well as in the cortical ventricular zone.
NOTE Confidence: 0.943838304444445

00:20:15.550 --> 00:20:17.950 But if you look in the cerebral cortex,
NOTE Confidence: 0.943838304444445

00:20:17.950 --> 00:20:19.990 it's only expressed in a subset of cells,
NOTE Confidence: 0.943838304444445

00:20:19.990 --> 00:20:22.062 And this was the first clue that it
NOTE Confidence: 0.943838304444445

00:20:22.062 --> 00:20:24.318 may be different in the inhibitory
NOTE Confidence: 0.943838304444445

00:20:24.318 --> 00:20:25.986 in the excitatory neurons.
NOTE Confidence: 0.943838304444445

00:20:25.990 --> 00:20:28.915 And it turns out that ARX is expressed in
NOTE Confidence: 0.943838304444445

00:20:28.915 --> 00:20:32.064 all of the ventricular zone of the cortex,
NOTE Confidence: 0.943838304444445

00:20:32.070 --> 00:20:34.222 but it turns off as soon as those
NOTE Confidence: 0.943838304444445

00:20:34.222 --> 00:20:35.748 cells exit the cell cycle.
NOTE Confidence: 0.943838304444445

00:20:35.750 --> 00:20:36.103 However,

NOTE Confidence: 0.943838304444445

00:20:36.103 --> 00:20:37.868 in the inhibitory neurons coming

NOTE Confidence: 0.943838304444445

00:20:37.868 --> 00:20:39.840 out of that ganglionic evidence.

NOTE Confidence: 0.943838304444445

00:20:39.840 --> 00:20:42.840 It stays on all the way into adulthood.

NOTE Confidence: 0.943838304444445

00:20:42.840 --> 00:20:45.240 So it seems to have different

NOTE Confidence: 0.943838304444445

00:20:45.240 --> 00:20:47.282 role differential roles in these

NOTE Confidence: 0.943838304444445

00:20:47.282 --> 00:20:49.466 two different stem cells all the

NOTE Confidence: 0.943838304444445

00:20:49.466 --> 00:20:51.640 way into the mature neuron.

NOTE Confidence: 0.943838304444445

00:20:51.640 --> 00:20:54.680 So to study this what we did is

NOTE Confidence: 0.943838304444445

00:20:54.680 --> 00:20:56.919 we generated a mouse that had

NOTE Confidence: 0.943838304444445

00:20:56.920 --> 00:20:59.237 a that that was a Flox mouse.

NOTE Confidence: 0.943838304444445

00:20:59.240 --> 00:21:01.160 It has we inserted crease it

NOTE Confidence: 0.943838304444445

00:21:01.160 --> 00:21:03.398 was on either side of Exxon two.

NOTE Confidence: 0.943838304444445

00:21:03.400 --> 00:21:05.787 Remember Exxon two at the beginning of

NOTE Confidence: 0.943838304444445

00:21:05.787 --> 00:21:08.277 the homeo domains when we remove Exxon 2.

NOTE Confidence: 0.943838304444445

00:21:08.280 --> 00:21:10.400 It actually everything else is out of frame.

NOTE Confidence: 0.943838304444445

00:21:10.400 --> 00:21:13.256 You have no homeo domain and we
NOTE Confidence: 0.943838304444445

00:21:13.256 --> 00:21:15.959 believe this is a null mutation.
NOTE Confidence: 0.943838304444445

00:21:15.960 --> 00:21:18.096 We could then cross this mouse
NOTE Confidence: 0.943838304444445

00:21:18.096 --> 00:21:20.645 that we generated with a variety of
NOTE Confidence: 0.943838304444445

00:21:20.645 --> 00:21:22.745 different Cree driver mice and we
NOTE Confidence: 0.943838304444445

00:21:22.745 --> 00:21:25.461 could remove a RX from just excitatory
NOTE Confidence: 0.943838304444445

00:21:25.461 --> 00:21:29.800 or just inhibitory mice, sorry cells.
NOTE Confidence: 0.943838304444445

00:21:29.800 --> 00:21:31.396 Now to take one step back,
NOTE Confidence: 0.943838304444445

00:21:31.400 --> 00:21:32.102 a knockout,
NOTE Confidence: 0.943838304444445

00:21:32.102 --> 00:21:34.910 A germline knockout had been made by Doctor
NOTE Confidence: 0.943838304444445

00:21:34.974 --> 00:21:37.396 Kitamura in Japan and that was lethal.
NOTE Confidence: 0.943838304444445

00:21:37.400 --> 00:21:38.942 So we couldn't study any later
NOTE Confidence: 0.943838304444445

00:21:38.942 --> 00:21:39.713 effects with it.
NOTE Confidence: 0.943838304444445

00:21:39.720 --> 00:21:41.862 So we wanted to really hone down
NOTE Confidence: 0.943838304444445

00:21:41.862 --> 00:21:43.600 on different regions of the brain.
NOTE Confidence: 0.943838304444445

00:21:43.600 --> 00:21:44.360 So that's what we did.

NOTE Confidence: 0.943838304444445
00:21:44.360 --> 00:21:47.438 So here we've crossed this mouse
NOTE Confidence: 0.943838304444445
00:21:47.440 --> 00:21:49.180 with one that expresses creed
NOTE Confidence: 0.943838304444445
00:21:49.180 --> 00:21:50.920 just in the ganglionic eminence.
NOTE Confidence: 0.943838304444445
00:21:50.920 --> 00:21:53.760 And so ARX is normal in these
NOTE Confidence: 0.943838304444445
00:21:53.760 --> 00:21:55.280 excitatory radially migrating cells,
NOTE Confidence: 0.943838304444445
00:21:55.280 --> 00:21:57.120 but it's completely absent
NOTE Confidence: 0.943838304444445
00:21:57.120 --> 00:21:58.960 from the ganglionic eminence.
NOTE Confidence: 0.943838304444445
00:21:58.960 --> 00:22:00.600 And when we do that,
NOTE Confidence: 0.943838304444445
00:22:00.600 --> 00:22:02.040 what we see and hopefully I'll
NOTE Confidence: 0.943838304444445
00:22:02.040 --> 00:22:03.000 get this to work.
NOTE Confidence: 0.905900966666667
00:22:06.440 --> 00:22:08.442 There we go. So on your left
NOTE Confidence: 0.905900966666667
00:22:08.442 --> 00:22:10.360 side is a normal brain.
NOTE Confidence: 0.905900966666667
00:22:10.360 --> 00:22:12.980 We've genetically labeled all the
NOTE Confidence: 0.905900966666667
00:22:12.980 --> 00:22:15.684 inhibitory neurons with a green dye
NOTE Confidence: 0.905900966666667
00:22:15.684 --> 00:22:17.798 GFP and you can see them migrating
NOTE Confidence: 0.905900966666667

00:22:17.798 --> 00:22:19.602 out of the ganglionic eminence
NOTE Confidence: 0.905900966666667

00:22:19.602 --> 00:22:21.756 up towards the cortex and then
NOTE Confidence: 0.905900966666667

00:22:21.819 --> 00:22:23.955 turning and going into the cortex.
NOTE Confidence: 0.905900966666667

00:22:23.960 --> 00:22:26.198 Now what happens in the mutant
NOTE Confidence: 0.905900966666667

00:22:26.200 --> 00:22:27.016 is that these cells,
NOTE Confidence: 0.905900966666667

00:22:27.016 --> 00:22:28.240 you don't see quite the connection,
NOTE Confidence: 0.905900966666667

00:22:28.240 --> 00:22:29.864 but they're migrating out
NOTE Confidence: 0.905900966666667

00:22:29.864 --> 00:22:31.520 of the ganglionic eminence,
NOTE Confidence: 0.905900966666667

00:22:31.520 --> 00:22:34.040 they're going up into the cortex.
NOTE Confidence: 0.905900966666667

00:22:34.040 --> 00:22:35.720 But I'm sorry going up door sleep,
NOTE Confidence: 0.905900966666667

00:22:35.720 --> 00:22:37.834 but they don't turn out of their
NOTE Confidence: 0.905900966666667

00:22:37.834 --> 00:22:40.119 stream and go out into the cortex.
NOTE Confidence: 0.905900966666667

00:22:40.120 --> 00:22:41.518 And also I don't know how
NOTE Confidence: 0.905900966666667

00:22:41.518 --> 00:22:42.680 well you can see it,
NOTE Confidence: 0.905900966666667

00:22:42.680 --> 00:22:44.175 but there's cells migrating out
NOTE Confidence: 0.905900966666667

00:22:44.175 --> 00:22:46.382 here in the marginal zone and those

NOTE Confidence: 0.905900966666667

00:22:46.382 --> 00:22:48.626 are completely absent from the ARX.

NOTE Confidence: 0.905900966666667

00:22:48.626 --> 00:22:50.736 So it's completely eliminated one

NOTE Confidence: 0.905900966666667

00:22:50.736 --> 00:22:52.923 stream of these inhibitory neurons

NOTE Confidence: 0.905900966666667

00:22:52.923 --> 00:22:55.877 and it's there's a defect in the

NOTE Confidence: 0.905900966666667

00:22:55.953 --> 00:22:58.248 migration of that other stream.

NOTE Confidence: 0.905900966666667

00:22:58.250 --> 00:22:59.810 Now when we study these mice,

NOTE Confidence: 0.905900966666667

00:22:59.810 --> 00:23:01.142 I can tell you the brain

NOTE Confidence: 0.905900966666667

00:23:01.142 --> 00:23:01.808 is structurally normal.

NOTE Confidence: 0.905900966666667

00:23:01.810 --> 00:23:02.770 This has all been published,

NOTE Confidence: 0.905900966666667

00:23:02.770 --> 00:23:04.450 so I'm not going to go through details.

NOTE Confidence: 0.905900966666667

00:23:04.450 --> 00:23:05.970 The brain is structurally normal.

NOTE Confidence: 0.905900966666667

00:23:05.970 --> 00:23:08.410 The corpus callosum is intact.

NOTE Confidence: 0.905900966666667

00:23:08.410 --> 00:23:11.090 The cell layers are intact.

NOTE Confidence: 0.905900966666667

00:23:11.090 --> 00:23:13.337 Every single one of these mice that

NOTE Confidence: 0.905900966666667

00:23:13.337 --> 00:23:15.262 we've tested has epilepsy from the

NOTE Confidence: 0.905900966666667

00:23:15.262 --> 00:23:17.590 very first time we can look at it.

NOTE Confidence: 0.905900966666667

00:23:17.590 --> 00:23:20.026 So they develop different types of epilepsy.

NOTE Confidence: 0.905900966666667

00:23:20.030 --> 00:23:22.284 We see these spikes and slow wave

NOTE Confidence: 0.905900966666667

00:23:22.284 --> 00:23:24.004 with an electrical decrement like

NOTE Confidence: 0.905900966666667

00:23:24.004 --> 00:23:26.426 here that's what you see in children

NOTE Confidence: 0.905900966666667

00:23:26.426 --> 00:23:28.390 with infantile spasm syndrome,

NOTE Confidence: 0.905900966666667

00:23:28.390 --> 00:23:30.946 exactly like what you see with

NOTE Confidence: 0.905900966666667

00:23:30.946 --> 00:23:32.224 the ARX mutations.

NOTE Confidence: 0.905900966666667

00:23:32.230 --> 00:23:34.105 These are these Jacksonian type

NOTE Confidence: 0.905900966666667

00:23:34.105 --> 00:23:35.980 seizures which start and then

NOTE Confidence: 0.905900966666667

00:23:36.043 --> 00:23:37.947 propagate throughout the brain.

NOTE Confidence: 0.905900966666667

00:23:37.950 --> 00:23:40.771 So we see an evolution and different

NOTE Confidence: 0.905900966666667

00:23:40.771 --> 00:23:43.029 types of seizures starting from

NOTE Confidence: 0.905900966666667

00:23:43.030 --> 00:23:45.424 the earliest time we can record it.

NOTE Confidence: 0.905900966666667

00:23:45.430 --> 00:23:47.998 So these mice all have seizures.

NOTE Confidence: 0.905900966666667

00:23:48.000 --> 00:23:51.280 And the brains, as I said,

NOTE Confidence: 0.905900966666667

00:23:51.280 --> 00:23:53.560 are completely normal.

NOTE Confidence: 0.905900966666667

00:23:53.560 --> 00:23:57.360 Now in contrast, if we remove a RX,

NOTE Confidence: 0.905900966666667

00:23:57.360 --> 00:23:59.760 instead of from the ganglionic Eminence,

NOTE Confidence: 0.905900966666667

00:23:59.760 --> 00:24:02.370 we remove it from the excited where

NOTE Confidence: 0.905900966666667

00:24:02.370 --> 00:24:04.595 the excitatory neurons are being

NOTE Confidence: 0.905900966666667

00:24:04.595 --> 00:24:07.320 derived using a different Cree driver,

NOTE Confidence: 0.905900966666667

00:24:07.320 --> 00:24:09.540 what we see is something

NOTE Confidence: 0.905900966666667

00:24:09.540 --> 00:24:10.428 completely different.

NOTE Confidence: 0.905900966666667

00:24:10.430 --> 00:24:12.182 Now what you see is that

NOTE Confidence: 0.905900966666667

00:24:12.182 --> 00:24:13.830 the the brains are small.

NOTE Confidence: 0.905900966666667

00:24:13.830 --> 00:24:15.954 Remember I told you the brains

NOTE Confidence: 0.905900966666667

00:24:15.954 --> 00:24:17.830 are structurally normal with the

NOTE Confidence: 0.905900966666667

00:24:17.830 --> 00:24:19.830 removal from the inhibitory neurons.

NOTE Confidence: 0.905900966666667

00:24:19.830 --> 00:24:21.390 The cortex is very thin,

NOTE Confidence: 0.905900966666667

00:24:21.390 --> 00:24:23.202 it's actually dislaminated and

NOTE Confidence: 0.905900966666667

00:24:23.202 --> 00:24:25.467 you have no corpus callosum.
NOTE Confidence: 0.905900966666667

00:24:25.470 --> 00:24:27.507 So here you can see a normal
NOTE Confidence: 0.905900966666667

00:24:27.507 --> 00:24:29.396 corpus callosum and here you see
NOTE Confidence: 0.905900966666667

00:24:29.396 --> 00:24:30.986 a genesis of corpus callosum.
NOTE Confidence: 0.905900966666667

00:24:30.990 --> 00:24:33.792 So by removing it from the
NOTE Confidence: 0.905900966666667

00:24:33.792 --> 00:24:35.660 excitatory projection neurons you
NOTE Confidence: 0.905900966666667

00:24:35.737 --> 00:24:38.147 get all the structural defects.
NOTE Confidence: 0.905900966666667

00:24:38.150 --> 00:24:40.229 That you get none of the epilepsy.
NOTE Confidence: 0.905900966666667

00:24:40.230 --> 00:24:41.586 We've looked at hundreds of mice.
NOTE Confidence: 0.905900966666667

00:24:41.590 --> 00:24:44.350 We've never seen a seizure.
NOTE Confidence: 0.905900966666667

00:24:44.350 --> 00:24:46.460 So now we're starting to
NOTE Confidence: 0.905900966666667

00:24:46.460 --> 00:24:48.483 distinguish where does the kind
NOTE Confidence: 0.905900966666667

00:24:48.483 --> 00:24:50.148 of cognitive behavioral and where
NOTE Confidence: 0.905900966666667

00:24:50.148 --> 00:24:52.460 do some of the other neurologic
NOTE Confidence: 0.905900966666667

00:24:52.460 --> 00:24:54.750 phenotypes where they derive from,
NOTE Confidence: 0.905900966666667

00:24:54.750 --> 00:24:56.425 from a cell migration standpoint

NOTE Confidence: 0.905900966666667

00:24:56.425 --> 00:24:58.100 and and this just shows.

NOTE Confidence: 0.905900966666667

00:24:58.100 --> 00:25:00.020 The disruption of the cortical lamination,

NOTE Confidence: 0.905900966666667

00:25:00.020 --> 00:25:03.188 we can look at at specific genes that

NOTE Confidence: 0.905900966666667

00:25:03.188 --> 00:25:05.561 are expressed in specific laminae

NOTE Confidence: 0.905900966666667

00:25:05.561 --> 00:25:07.553 and show defects predominantly

NOTE Confidence: 0.905900966666667

00:25:07.553 --> 00:25:10.060 in the upper layer cells.

NOTE Confidence: 0.905900966666667

00:25:10.060 --> 00:25:12.300 And those upper layer cells in the

NOTE Confidence: 0.9553487

00:25:12.300 --> 00:25:14.500 mouse come from those intermediate

NOTE Confidence: 0.9553487

00:25:14.500 --> 00:25:16.700 progenitor cells that I mentioned.

NOTE Confidence: 0.9553487

00:25:16.700 --> 00:25:18.940 And so we looked at those intermediate

NOTE Confidence: 0.9553487

00:25:18.940 --> 00:25:20.660 progenitor cells and what we found

NOTE Confidence: 0.9553487

00:25:20.660 --> 00:25:23.516 doing single cell is that they are

NOTE Confidence: 0.9553487

00:25:23.516 --> 00:25:26.600 missing something called CDKN 1C.

NOTE Confidence: 0.9553487

00:25:26.600 --> 00:25:29.720 ARX is regulating CDKN 1C,

NOTE Confidence: 0.9553487

00:25:29.720 --> 00:25:31.484 and that's a gene that's important for

NOTE Confidence: 0.9553487

00:25:31.484 --> 00:25:33.478 cells being able to reenter the cell cycle.
NOTE Confidence: 0.9553487

00:25:33.480 --> 00:25:35.358 So what's happening is these cells,
NOTE Confidence: 0.9553487

00:25:35.360 --> 00:25:38.940 because they no longer express the CDKN 1C,
NOTE Confidence: 0.9553487

00:25:38.940 --> 00:25:42.000 are exiting the cell cycle prematurely.
NOTE Confidence: 0.9553487

00:25:42.000 --> 00:25:44.525 Therefore you're not getting the
NOTE Confidence: 0.9553487

00:25:44.525 --> 00:25:47.640 correct number of of rounds of mitosis
NOTE Confidence: 0.9553487

00:25:47.640 --> 00:25:49.240 in the intermediate progenitor
NOTE Confidence: 0.9553487

00:25:49.240 --> 00:25:51.972 cell and you've got a defect in
NOTE Confidence: 0.9553487

00:25:51.972 --> 00:25:53.837 those mostly upper layer neurons.
NOTE Confidence: 0.934383218333333

00:25:55.900 --> 00:25:59.284 We can actually test that by going in
NOTE Confidence: 0.934383218333333

00:25:59.284 --> 00:26:02.740 and we built a a system to actually
NOTE Confidence: 0.934383218333333

00:26:02.740 --> 00:26:04.580 repress actually what happened.
NOTE Confidence: 0.934383218333333

00:26:04.580 --> 00:26:05.840 Sorry, I just misspoke.
NOTE Confidence: 0.934383218333333

00:26:05.840 --> 00:26:07.988 There's over expression of the CDKN 1C.
NOTE Confidence: 0.934383218333333

00:26:07.988 --> 00:26:09.976 The ARX is a repressor of that.
NOTE Confidence: 0.934383218333333

00:26:09.980 --> 00:26:12.689 We then knocked it down and we can see

NOTE Confidence: 0.934383218333333

00:26:12.689 --> 00:26:15.603 the return of the proliferation and we

NOTE Confidence: 0.934383218333333

00:26:15.603 --> 00:26:18.301 actually can rescue that phenotype of

NOTE Confidence: 0.934383218333333

00:26:18.301 --> 00:26:21.097 loss of the mostly superficial neurons.

NOTE Confidence: 0.934383218333333

00:26:21.100 --> 00:26:23.746 So this showed that that was one of the

NOTE Confidence: 0.934383218333333

00:26:23.746 --> 00:26:25.618 mechanisms by which ARX was functioning.

NOTE Confidence: 0.931867333333333

00:26:28.470 --> 00:26:31.068 So with this all in mind,

NOTE Confidence: 0.931867333333333

00:26:31.070 --> 00:26:32.840 I want to turn our attention

NOTE Confidence: 0.931867333333333

00:26:32.840 --> 00:26:34.890 to this set of two kids.

NOTE Confidence: 0.931867333333333

00:26:34.890 --> 00:26:37.692 Now at the top is a child

NOTE Confidence: 0.931867333333333

00:26:37.692 --> 00:26:40.227 who has an ARX mutation.

NOTE Confidence: 0.931867333333333

00:26:40.230 --> 00:26:43.052 And that mutation, that child has had

NOTE Confidence: 0.931867333333333

00:26:43.052 --> 00:26:45.344 epilepsy starting at about six months

NOTE Confidence: 0.931867333333333

00:26:45.350 --> 00:26:47.374 in severe intellectual disabilities,

NOTE Confidence: 0.931867333333333

00:26:47.374 --> 00:26:50.410 never was able to feed himself.

NOTE Confidence: 0.931867333333333

00:26:50.410 --> 00:26:52.545 And you can see has the so-called

NOTE Confidence: 0.931867333333333

00:26:52.545 --> 00:26:54.185 lizencephaly, the smooth brain
NOTE Confidence: 0.9318673333333333

00:26:54.185 --> 00:26:55.965 Lysos meaning smooth encephaly,
NOTE Confidence: 0.9318673333333333

00:26:55.970 --> 00:26:57.048 brain lizencephaly.
NOTE Confidence: 0.9318673333333333

00:26:57.048 --> 00:26:59.743 And you can see predominantly
NOTE Confidence: 0.9318673333333333

00:26:59.743 --> 00:27:01.850 in this posterior part.
NOTE Confidence: 0.9318673333333333

00:27:01.850 --> 00:27:04.886 There's no suicide here at all.
NOTE Confidence: 0.9318673333333333

00:27:04.890 --> 00:27:06.770 Here you can see posteriorly.
NOTE Confidence: 0.9318673333333333

00:27:06.770 --> 00:27:09.962 Now the child at the bottom also has
NOTE Confidence: 0.9318673333333333

00:27:09.962 --> 00:27:12.971 an ARX mutation, also had epilepsy.
NOTE Confidence: 0.9318673333333333

00:27:12.971 --> 00:27:16.839 It didn't start till about 9 to 10 months
NOTE Confidence: 0.9318673333333333

00:27:16.839 --> 00:27:19.544 and had severe intellectual disability.
NOTE Confidence: 0.9318673333333333

00:27:19.550 --> 00:27:23.906 But this brain is structurally normal.
NOTE Confidence: 0.9318673333333333

00:27:23.910 --> 00:27:27.213 The brain of the child at the top had
NOTE Confidence: 0.9318673333333333

00:27:27.213 --> 00:27:30.938 a truncation mutation loss of a RX.
NOTE Confidence: 0.9318673333333333

00:27:30.938 --> 00:27:33.885 The child at the bottom had an
NOTE Confidence: 0.9318673333333333

00:27:33.885 --> 00:27:36.469 alanine tract expansion mutation.

NOTE Confidence: 0.9318673333333333
00:27:36.470 --> 00:27:39.470 Now if we think about what I just told you,
NOTE Confidence: 0.9318673333333333
00:27:39.470 --> 00:27:41.110 the brain is structurally normal,
NOTE Confidence: 0.9318673333333333
00:27:41.110 --> 00:27:44.142 but you have the seizures if you have
NOTE Confidence: 0.9318673333333333
00:27:44.142 --> 00:27:47.208 a defect in your inhibitory neurons.
NOTE Confidence: 0.9318673333333333
00:27:47.210 --> 00:27:48.218 But it's only when you have
NOTE Confidence: 0.9318673333333333
00:27:48.218 --> 00:27:49.330 a defect in the migration,
NOTE Confidence: 0.9318673333333333
00:27:49.330 --> 00:27:52.048 the movement of those excitatory neurons
NOTE Confidence: 0.9318673333333333
00:27:52.050 --> 00:27:54.888 that you have the structural defects.
NOTE Confidence: 0.9318673333333333
00:27:54.890 --> 00:27:56.546 So we predicted that that's what
NOTE Confidence: 0.9318673333333333
00:27:56.546 --> 00:27:58.568 we would see if we tested this.
NOTE Confidence: 0.9318673333333333
00:27:58.570 --> 00:28:02.170 So that's what we did experimentally.
NOTE Confidence: 0.9318673333333333
00:28:02.170 --> 00:28:03.650 So to do these experiments,
NOTE Confidence: 0.9318673333333333
00:28:03.650 --> 00:28:05.369 we went in and and you can do something
NOTE Confidence: 0.9318673333333333
00:28:05.369 --> 00:28:06.608 called in utero electroporation.
NOTE Confidence: 0.9318673333333333
00:28:06.610 --> 00:28:09.290 This is where you can take a mouse,
NOTE Confidence: 0.9318673333333333

00:28:09.290 --> 00:28:10.658 a gravid mom,
NOTE Confidence: 0.9318673333333333

00:28:10.658 --> 00:28:12.938 you can exteriorize the uterus.
NOTE Confidence: 0.9318673333333333

00:28:12.940 --> 00:28:15.664 You can go in and check some of
NOTE Confidence: 0.9318673333333333

00:28:15.664 --> 00:28:17.884 an expression construct into the
NOTE Confidence: 0.9318673333333333

00:28:17.884 --> 00:28:20.264 ventricle of the into the pup while
NOTE Confidence: 0.9318673333333333

00:28:20.264 --> 00:28:22.238 it's in the uterus and you put
NOTE Confidence: 0.9318673333333333

00:28:22.238 --> 00:28:23.978 these electrodes on either side,
NOTE Confidence: 0.9318673333333333

00:28:23.980 --> 00:28:25.200 you electroplate it just like
NOTE Confidence: 0.9318673333333333

00:28:25.200 --> 00:28:26.420 you would in a gel.
NOTE Confidence: 0.9318673333333333

00:28:26.420 --> 00:28:29.276 The DNA goes into the brain and then
NOTE Confidence: 0.9318673333333333

00:28:29.276 --> 00:28:32.275 you can actually return the grab the
NOTE Confidence: 0.9318673333333333

00:28:32.275 --> 00:28:34.060 uterus back into the mom sewer up
NOTE Confidence: 0.9318673333333333

00:28:34.060 --> 00:28:36.334 and those mice can go on and even be
NOTE Confidence: 0.9318673333333333

00:28:36.334 --> 00:28:38.578 delivered so we can study them later
NOTE Confidence: 0.9318673333333333

00:28:38.580 --> 00:28:41.650 and what you see is if you do that normally.
NOTE Confidence: 0.9318673333333333

00:28:41.650 --> 00:28:43.526 The cells migrate out to the cortex.

NOTE Confidence: 0.9318673333333333
00:28:43.530 --> 00:28:46.078 So this is just with the GFP
NOTE Confidence: 0.9318673333333333
00:28:46.078 --> 00:28:48.248 electroporated into our ARX Flox mice,
NOTE Confidence: 0.9318673333333333
00:28:48.250 --> 00:28:49.278 no Cree.
NOTE Confidence: 0.9318673333333333
00:28:49.278 --> 00:28:51.848 So they're just wild type.
NOTE Confidence: 0.9318673333333333
00:28:51.850 --> 00:28:54.025 If we introduce a brain
NOTE Confidence: 0.9318673333333333
00:28:54.025 --> 00:28:56.674 four or this how 3F4 Cree.
NOTE Confidence: 0.9318673333333333
00:28:56.674 --> 00:29:00.250 What you see when you electroporate in GFP,
NOTE Confidence: 0.9318673333333333
00:29:00.250 --> 00:29:02.567 now they've lost all of their ARX.
NOTE Confidence: 0.9318673333333333
00:29:02.570 --> 00:29:05.727 You see that these cells don't migrate.
NOTE Confidence: 0.9318673333333333
00:29:05.730 --> 00:29:08.484 If we rescue this with a wild type ARX,
NOTE Confidence: 0.9318673333333333
00:29:08.490 --> 00:29:10.488 you see the cells migrate out to the surface,
NOTE Confidence: 0.9318673333333333
00:29:10.490 --> 00:29:11.930 just not very nicely.
NOTE Confidence: 0.9318673333333333
00:29:11.930 --> 00:29:14.090 You have a very nice rescue.
NOTE Confidence: 0.9318673333333333
00:29:14.090 --> 00:29:16.570 But if you do that with the sorry,
NOTE Confidence: 0.9318673333333333
00:29:16.570 --> 00:29:18.723 and if you do that with the ARX
NOTE Confidence: 0.9318673333333333

00:29:18.723 --> 00:29:21.088 that has that expansion mutation,
NOTE Confidence: 0.9318673333333333

00:29:21.090 --> 00:29:23.286 you also rescue that radial migration.
NOTE Confidence: 0.9318673333333333

00:29:23.290 --> 00:29:25.649 These cells migrate out to the surface.
NOTE Confidence: 0.9318673333333333

00:29:25.650 --> 00:29:27.990 So the expansion mutation doesn't seem
NOTE Confidence: 0.9318673333333333

00:29:27.990 --> 00:29:30.090 to affect these excitatory neurons,
NOTE Confidence: 0.9318673333333333

00:29:30.090 --> 00:29:31.805 at least their ability to migrate out.
NOTE Confidence: 0.95175457

00:29:35.660 --> 00:29:38.138 Now contrast that to the inhibitory neurons.
NOTE Confidence: 0.95175457

00:29:38.140 --> 00:29:40.534 So now what we've done is when you put
NOTE Confidence: 0.95175457

00:29:40.534 --> 00:29:42.724 it in the wild type, the cells migrate
NOTE Confidence: 0.95175457

00:29:42.724 --> 00:29:44.460 out very nicely up into the cortex.
NOTE Confidence: 0.95175457

00:29:44.460 --> 00:29:46.480 So now we've just electroplate
NOTE Confidence: 0.95175457

00:29:46.480 --> 00:29:48.096 into the ganglionic eminence.
NOTE Confidence: 0.95175457

00:29:48.100 --> 00:29:50.494 The cells migrate up when you put it in,
NOTE Confidence: 0.95175457

00:29:50.500 --> 00:29:53.056 when you remove a RX from the whole brain,
NOTE Confidence: 0.95175457

00:29:53.060 --> 00:29:54.190 you see that these cells
NOTE Confidence: 0.95175457

00:29:54.190 --> 00:29:55.094 no longer migrate up.

NOTE Confidence: 0.95175457
00:29:55.100 --> 00:29:57.396 They kind of get stuck down here
NOTE Confidence: 0.95175457
00:29:57.396 --> 00:29:59.620 in what will become striatum.
NOTE Confidence: 0.95175457
00:29:59.620 --> 00:30:02.300 If we rescue with the wild type ARX,
NOTE Confidence: 0.95175457
00:30:02.300 --> 00:30:04.246 you can see that again these cells
NOTE Confidence: 0.95175457
00:30:04.246 --> 00:30:05.800 are migrating up very nicely.
NOTE Confidence: 0.95175457
00:30:05.800 --> 00:30:07.560 Yeah, you can see that.
NOTE Confidence: 0.95175457
00:30:07.560 --> 00:30:09.310 But if we do that with the
NOTE Confidence: 0.95175457
00:30:09.310 --> 00:30:10.560 alanine tract expansion mutation,
NOTE Confidence: 0.95175457
00:30:10.560 --> 00:30:12.800 they don't.
NOTE Confidence: 0.95175457
00:30:12.800 --> 00:30:16.106 So the alanine tract expansion seems
NOTE Confidence: 0.95175457
00:30:16.106 --> 00:30:18.740 to be differentially affecting
NOTE Confidence: 0.95175457
00:30:18.740 --> 00:30:22.625 the inhibitory neurons and a whole
NOTE Confidence: 0.95175457
00:30:22.625 --> 00:30:24.515 series of experiments that we did,
NOTE Confidence: 0.95175457
00:30:24.520 --> 00:30:27.810 we went on to show that it was due to
NOTE Confidence: 0.95175457
00:30:27.906 --> 00:30:31.466 the ability of a RX and Progenitor cells
NOTE Confidence: 0.95175457

00:30:31.466 --> 00:30:35.568 to affect different transcriptional pathways.

NOTE Confidence: 0.95175457

00:30:35.570 --> 00:30:37.610 So in the inhibitory neurons,

NOTE Confidence: 0.95175457

00:30:37.610 --> 00:30:39.165 what happens when you have

NOTE Confidence: 0.95175457

00:30:39.165 --> 00:30:40.409 an alanine tract expansion?

NOTE Confidence: 0.95175457

00:30:40.410 --> 00:30:41.730 Remember transcription isn't

NOTE Confidence: 0.95175457

00:30:41.730 --> 00:30:43.930 isolated to 1 transcription factor,

NOTE Confidence: 0.95175457

00:30:43.930 --> 00:30:46.030 it's a transcriptional complex usually

NOTE Confidence: 0.95175457

00:30:46.030 --> 00:30:48.810 with 40 to 60 different proteins.

NOTE Confidence: 0.95175457

00:30:48.810 --> 00:30:51.230 And so this complex usually

NOTE Confidence: 0.95175457

00:30:51.230 --> 00:30:53.166 has stabilizers and cofactors.

NOTE Confidence: 0.95175457

00:30:53.170 --> 00:30:56.176 And what happens in the we showed

NOTE Confidence: 0.95175457

00:30:56.176 --> 00:30:57.754 through Co immunoprecipitation.

NOTE Confidence: 0.95175457

00:30:57.754 --> 00:31:01.905 This complex falls apart and this T LE1

NOTE Confidence: 0.95175457

00:31:01.905 --> 00:31:04.665 which is a gaucho like transcriptional

NOTE Confidence: 0.95175457

00:31:04.665 --> 00:31:06.575 repressor involved in repressing

NOTE Confidence: 0.95175457

00:31:06.575 --> 00:31:10.112 things like Ed F3 and also that CDKN

NOTE Confidence: 0.95175457

00:31:10.112 --> 00:31:13.808 1C that I mentioned no longer get repressed.

NOTE Confidence: 0.95175457

00:31:13.810 --> 00:31:16.302 They continue to be overexpressed and that

NOTE Confidence: 0.95175457

00:31:16.302 --> 00:31:19.010 leads to defects in these inhibitory norms.

NOTE Confidence: 0.95175457

00:31:19.010 --> 00:31:19.661 However,

NOTE Confidence: 0.95175457

00:31:19.661 --> 00:31:21.614 the transcriptional complex

NOTE Confidence: 0.95175457

00:31:21.614 --> 00:31:23.567 is structurally different.

NOTE Confidence: 0.95175457

00:31:23.570 --> 00:31:25.235 In the excitatory neurons such

NOTE Confidence: 0.95175457

00:31:25.235 --> 00:31:27.339 that even with that polyne alanine

NOTE Confidence: 0.95175457

00:31:27.339 --> 00:31:29.583 tract expansion that leads to a

NOTE Confidence: 0.95175457

00:31:29.583 --> 00:31:31.529 conformational change in this protein,

NOTE Confidence: 0.95175457

00:31:31.530 --> 00:31:34.890 you still get the structure of this,

NOTE Confidence: 0.95175457

00:31:34.890 --> 00:31:37.285 the cofactors coming together and

NOTE Confidence: 0.95175457

00:31:37.285 --> 00:31:39.680 it still can repress molecules

NOTE Confidence: 0.95175457

00:31:39.758 --> 00:31:42.740 like LMO one which are required for

NOTE Confidence: 0.95175457

00:31:42.740 --> 00:31:44.850 the excitatory neuron migration.

NOTE Confidence: 0.95175457

00:31:44.850 --> 00:31:47.433 And so this shows how this one
NOTE Confidence: 0.95175457

00:31:47.433 --> 00:31:49.034 transcription factor with a
NOTE Confidence: 0.95175457

00:31:49.034 --> 00:31:51.174 single mutation can have different
NOTE Confidence: 0.95175457

00:31:51.174 --> 00:31:52.886 functions in different cell,
NOTE Confidence: 0.95175457

00:31:52.890 --> 00:31:54.810 in different progenitor cells
NOTE Confidence: 0.95175457

00:31:54.810 --> 00:31:56.730 leading to different phenotypes.
NOTE Confidence: 0.95175457

00:31:56.730 --> 00:31:59.778 Whereas in in if you remove a RX
NOTE Confidence: 0.95175457

00:31:59.778 --> 00:32:02.410 it'll affect both of them together
NOTE Confidence: 0.95175457

00:32:02.410 --> 00:32:04.695 and that's what happens with
NOTE Confidence: 0.95175457

00:32:04.695 --> 00:32:06.523 the Liz encephaly phenotype.
NOTE Confidence: 0.95175457

00:32:06.530 --> 00:32:10.592 Now we went on to take a non
NOTE Confidence: 0.95175457

00:32:10.592 --> 00:32:13.147 unbiased proteomics approach to say.
NOTE Confidence: 0.95175457

00:32:13.150 --> 00:32:14.190 Wow, this is really interesting.
NOTE Confidence: 0.95175457

00:32:14.190 --> 00:32:15.370 What are all the proteins
NOTE Confidence: 0.95175457

00:32:15.370 --> 00:32:16.550 that interact with a RX?
NOTE Confidence: 0.95175457

00:32:16.550 --> 00:32:19.287 Because we want to understand that whole

NOTE Confidence: 0.95175457

00:32:19.287 --> 00:32:21.108 transcriptional complex and we actually

NOTE Confidence: 0.95175457

00:32:21.108 --> 00:32:23.184 uncovered a number of different proteins.

NOTE Confidence: 0.95175457

00:32:23.190 --> 00:32:25.845 But unfortunately we were really

NOTE Confidence: 0.95175457

00:32:25.845 --> 00:32:27.801 looking for other transcription factors

NOTE Confidence: 0.95175457

00:32:27.801 --> 00:32:29.583 that are interacting with a RX,

NOTE Confidence: 0.95175457

00:32:29.590 --> 00:32:30.654 and I'm going to come back to

NOTE Confidence: 0.95175457

00:32:30.654 --> 00:32:31.430 that in a minute.

NOTE Confidence: 0.95175457

00:32:31.430 --> 00:32:33.201 What we did find is a number

NOTE Confidence: 0.95175457

00:32:33.201 --> 00:32:34.868 of things that are involved in

NOTE Confidence: 0.95175457

00:32:34.868 --> 00:32:36.434 the when signaling pathway,

NOTE Confidence: 0.95175457

00:32:36.434 --> 00:32:38.574 which is important for proliferation

NOTE Confidence: 0.95175457

00:32:38.574 --> 00:32:40.492 in those cortical ventricular cells.

NOTE Confidence: 0.95175457

00:32:40.492 --> 00:32:42.970 So I'm not going to that's that's

NOTE Confidence: 0.95175457

00:32:43.034 --> 00:32:44.078 work we published.

NOTE Confidence: 0.95175457

00:32:44.080 --> 00:32:45.800 I'm not going to talk about it today.

NOTE Confidence: 0.95175457

00:32:45.800 --> 00:32:49.363 But we also found that it affected
NOTE Confidence: 0.95175457

00:32:49.363 --> 00:32:52.078 dorsal ventral patterning in the brain.
NOTE Confidence: 0.935608953846154

00:32:52.080 --> 00:32:55.491 So if you take the brain and this is
NOTE Confidence: 0.935608953846154

00:32:55.491 --> 00:32:57.651 expression of Olig 2, some work we
NOTE Confidence: 0.935608953846154

00:32:57.651 --> 00:32:59.818 published just a few years ago here
NOTE Confidence: 0.935608953846154

00:32:59.818 --> 00:33:03.220 you can see a very nice border where a
NOTE Confidence: 0.935608953846154

00:33:03.314 --> 00:33:06.658 RX is normally sorry where all Olig 2.
NOTE Confidence: 0.935608953846154

00:33:06.660 --> 00:33:08.796 Stops being expressed, and you can
NOTE Confidence: 0.935608953846154

00:33:08.796 --> 00:33:11.236 see that here in the coronal plane.
NOTE Confidence: 0.935608953846154

00:33:11.236 --> 00:33:14.896 And if you look at it in the sagittal plane,
NOTE Confidence: 0.935608953846154

00:33:14.896 --> 00:33:18.528 you can see that it stops at the top of
NOTE Confidence: 0.935608953846154

00:33:18.528 --> 00:33:21.336 that gang, that lateral ganglionic eminence.
NOTE Confidence: 0.935608953846154

00:33:21.340 --> 00:33:23.500 But that's not what happens
NOTE Confidence: 0.935608953846154

00:33:23.500 --> 00:33:24.856 in the ARX mutant.
NOTE Confidence: 0.935608953846154

00:33:24.856 --> 00:33:27.260 You can see that this olive two,
NOTE Confidence: 0.935608953846154

00:33:27.260 --> 00:33:29.160 normally only expressed in the

NOTE Confidence: 0.935608953846154

00:33:29.160 --> 00:33:31.060 ventral part of the brain,

NOTE Confidence: 0.935608953846154

00:33:31.060 --> 00:33:33.168 is now expressed extensively

NOTE Confidence: 0.935608953846154

00:33:33.168 --> 00:33:35.276 across the dorsal cortex.

NOTE Confidence: 0.935608953846154

00:33:35.280 --> 00:33:37.872 And you can see it going up beyond where

NOTE Confidence: 0.935608953846154

00:33:37.872 --> 00:33:41.216 we would normally see it in the wild type.

NOTE Confidence: 0.935608953846154

00:33:41.216 --> 00:33:43.580 So this suggested that in addition

NOTE Confidence: 0.935608953846154

00:33:43.665 --> 00:33:45.637 to a proliferation effect,

NOTE Confidence: 0.935608953846154

00:33:45.640 --> 00:33:48.797 it was affecting patterning of the brain.

NOTE Confidence: 0.935608953846154

00:33:48.800 --> 00:33:51.880 So what's important about that?

NOTE Confidence: 0.935608953846154

00:33:51.880 --> 00:33:53.736 Oh, so we went on and showed that

NOTE Confidence: 0.935608953846154

00:33:53.736 --> 00:33:55.478 it's not just the wing pathway,

NOTE Confidence: 0.935608953846154

00:33:55.480 --> 00:33:56.892 but it's also FGFA.

NOTE Confidence: 0.935608953846154

00:33:56.892 --> 00:33:59.010 And Sonic Hedgehog and we basically

NOTE Confidence: 0.935608953846154

00:33:59.081 --> 00:34:01.419 were able to separate out all these

NOTE Confidence: 0.935608953846154

00:34:01.419 --> 00:34:03.689 pathways and how that was affecting

NOTE Confidence: 0.935608953846154

00:34:03.689 --> 00:34:06.089 all of two and downstream components.
NOTE Confidence: 0.935608953846154

00:34:06.090 --> 00:34:06.316 Again,
NOTE Confidence: 0.935608953846154

00:34:06.316 --> 00:34:08.124 these are not things I'm going to talk
NOTE Confidence: 0.935608953846154

00:34:08.124 --> 00:34:09.730 about today in the interest of time.
NOTE Confidence: 0.935608953846154

00:34:09.730 --> 00:34:11.146 But what we,
NOTE Confidence: 0.935608953846154

00:34:11.146 --> 00:34:13.506 the reason we became interested
NOTE Confidence: 0.935608953846154

00:34:13.506 --> 00:34:16.448 in this patterning is because
NOTE Confidence: 0.935608953846154

00:34:16.450 --> 00:34:19.467 these mice as I've alluded to have
NOTE Confidence: 0.935608953846154

00:34:19.467 --> 00:34:21.452 behavioral defects and we wanted
NOTE Confidence: 0.935608953846154

00:34:21.452 --> 00:34:23.322 to understand what's the biologic
NOTE Confidence: 0.935608953846154

00:34:23.322 --> 00:34:25.820 basis of these behavioral defects.
NOTE Confidence: 0.935608953846154

00:34:25.820 --> 00:34:28.412 So it turns out that and again some studies
NOTE Confidence: 0.935608953846154

00:34:28.412 --> 00:34:30.891 we did a few years ago back in 2014,
NOTE Confidence: 0.935608953846154

00:34:30.891 --> 00:34:33.046 we showed that these mice
NOTE Confidence: 0.935608953846154

00:34:33.046 --> 00:34:34.339 have normal strength.
NOTE Confidence: 0.935608953846154

00:34:34.340 --> 00:34:36.060 We had they have a lot of they,

NOTE Confidence: 0.935608953846154

00:34:36.060 --> 00:34:38.970 they have normal ability to recognize

NOTE Confidence: 0.935608953846154

00:34:38.970 --> 00:34:41.450 things in a remember things in a swim

NOTE Confidence: 0.935608953846154

00:34:41.450 --> 00:34:43.615 test when you do Morris water maze.

NOTE Confidence: 0.935608953846154

00:34:43.620 --> 00:34:45.540 But they're socially abnormal.

NOTE Confidence: 0.935608953846154

00:34:45.540 --> 00:34:48.915 And this is typical of mice that are

NOTE Confidence: 0.935608953846154

00:34:48.915 --> 00:34:51.340 believed to be in the human equivalent

NOTE Confidence: 0.935608953846154

00:34:51.340 --> 00:34:53.340 of the autism spectrum disorder,

NOTE Confidence: 0.935608953846154

00:34:53.340 --> 00:34:56.940 which as I said is part of the ARX phenotype.

NOTE Confidence: 0.935608953846154

00:34:56.940 --> 00:34:58.796 And so here the I'm just going to

NOTE Confidence: 0.935608953846154

00:34:58.796 --> 00:35:00.202 show you one socialization test

NOTE Confidence: 0.935608953846154

00:35:00.202 --> 00:35:02.592 we did where you you take this is

NOTE Confidence: 0.935608953846154

00:35:02.592 --> 00:35:04.004 called the novel mouse experiment

NOTE Confidence: 0.935608953846154

00:35:04.004 --> 00:35:06.436 and where you what you do is you

NOTE Confidence: 0.935608953846154

00:35:06.436 --> 00:35:08.709 put one mouse in this plexiglass

NOTE Confidence: 0.935608953846154

00:35:08.709 --> 00:35:10.614 thing with these little holes.

NOTE Confidence: 0.935608953846154

00:35:10.620 --> 00:35:12.223 And you put in the other side
NOTE Confidence: 0.935608953846154

00:35:12.223 --> 00:35:14.069 of it and either an empty one
NOTE Confidence: 0.935608953846154

00:35:14.069 --> 00:35:15.512 of these or an inanimate object,
NOTE Confidence: 0.935608953846154

00:35:15.512 --> 00:35:17.123 you can put like a stuffed animal
NOTE Confidence: 0.935608953846154

00:35:17.123 --> 00:35:18.497 or something like that in it.
NOTE Confidence: 0.935608953846154

00:35:18.500 --> 00:35:20.460 And this is the test mouse right here.
NOTE Confidence: 0.935608953846154

00:35:20.460 --> 00:35:23.020 And this mouse has never seen this mouse.
NOTE Confidence: 0.935608953846154

00:35:23.020 --> 00:35:23.794 They're social creatures.
NOTE Confidence: 0.935608953846154

00:35:23.794 --> 00:35:25.342 They're going to go and interact
NOTE Confidence: 0.935608953846154

00:35:25.342 --> 00:35:26.100 with each other.
NOTE Confidence: 0.935608953846154

00:35:26.100 --> 00:35:27.402 And you can see that when you
NOTE Confidence: 0.935608953846154

00:35:27.402 --> 00:35:28.499 put in these novel mice,
NOTE Confidence: 0.935608953846154

00:35:28.500 --> 00:35:31.380 the the blue bar shows you how much time,
NOTE Confidence: 0.935608953846154

00:35:31.380 --> 00:35:33.865 the percent of time that they're spending
NOTE Confidence: 0.935608953846154

00:35:33.865 --> 00:35:36.249 with that novel with that new mouse.
NOTE Confidence: 0.935608953846154

00:35:36.250 --> 00:35:38.770 Whereas the mutants don't do that.

NOTE Confidence: 0.935608953846154

00:35:38.770 --> 00:35:40.429 So they've got a socialization defect and

NOTE Confidence: 0.935608953846154

00:35:40.429 --> 00:35:42.288 we showed that through several different,

NOTE Confidence: 0.935608953846154

00:35:42.290 --> 00:35:45.450 but like I said this is just one of those.

NOTE Confidence: 0.945285241666667

00:35:45.450 --> 00:35:47.808 So coming back to this patterning,

NOTE Confidence: 0.945285241666667

00:35:47.810 --> 00:35:49.826 this was really interesting to us because

NOTE Confidence: 0.945285241666667

00:35:49.826 --> 00:35:52.142 if you look at patterning dorsal ventral

NOTE Confidence: 0.945285241666667

00:35:52.142 --> 00:35:54.629 patterning in the spinal cord where it's

NOTE Confidence: 0.945285241666667

00:35:54.629 --> 00:35:58.082 been best elucidated work by Tom Jessel

NOTE Confidence: 0.945285241666667

00:35:58.082 --> 00:36:01.696 and James Briscoe and others, many others.

NOTE Confidence: 0.945285241666667

00:36:01.700 --> 00:36:04.148 What what we now know is that there's

NOTE Confidence: 0.945285241666667

00:36:04.148 --> 00:36:06.784 specific cell types that come from different

NOTE Confidence: 0.945285241666667

00:36:06.784 --> 00:36:08.739 regions along the progenitor zone,

NOTE Confidence: 0.945285241666667

00:36:08.740 --> 00:36:11.340 from dorsal to ventral in the spinal cord,

NOTE Confidence: 0.945285241666667

00:36:11.340 --> 00:36:15.076 and that these are defined by Sonic hedgehog

NOTE Confidence: 0.945285241666667

00:36:15.076 --> 00:36:17.700 expressed out of the notochord and then

NOTE Confidence: 0.945285241666667

00:36:17.766 --> 00:36:20.259 in the floor plate and on the roof plate,
NOTE Confidence: 0.945285241666667

00:36:20.260 --> 00:36:21.880 BMP's and wins,
NOTE Confidence: 0.945285241666667

00:36:21.880 --> 00:36:25.633 and these both induce and repress.
NOTE Confidence: 0.945285241666667

00:36:25.633 --> 00:36:27.766 Different transcription factors,
NOTE Confidence: 0.945285241666667

00:36:27.770 --> 00:36:30.590 setting up these different domains
NOTE Confidence: 0.945285241666667

00:36:30.590 --> 00:36:33.410 along the dorsal ventral axis.
NOTE Confidence: 0.945285241666667

00:36:33.410 --> 00:36:36.186 And the same thing seems to be happening
NOTE Confidence: 0.945285241666667

00:36:36.186 --> 00:36:38.650 in setting up different domains in
NOTE Confidence: 0.945285241666667

00:36:38.650 --> 00:36:40.770 the cerebral cortex that define,
NOTE Confidence: 0.945285241666667

00:36:40.770 --> 00:36:44.410 as I mentioned before, where the thalamic,
NOTE Confidence: 0.945285241666667

00:36:44.410 --> 00:36:45.301 thalamic cortical projections
NOTE Confidence: 0.945285241666667

00:36:45.301 --> 00:36:46.489 are going to be.
NOTE Confidence: 0.945285241666667

00:36:46.490 --> 00:36:48.008 So you're getting your, you know,
NOTE Confidence: 0.945285241666667

00:36:48.010 --> 00:36:49.662 visual cortex back here.
NOTE Confidence: 0.945285241666667

00:36:49.662 --> 00:36:51.727 You get your motor cortex,
NOTE Confidence: 0.945285241666667

00:36:51.730 --> 00:36:53.170 your sensory cortex.

NOTE Confidence: 0.945285241666667
00:36:53.170 --> 00:36:55.570 All of these primary cortices
NOTE Confidence: 0.945285241666667
00:36:55.570 --> 00:36:58.029 are coming out of definition,
NOTE Confidence: 0.945285241666667
00:36:58.030 --> 00:37:00.046 and that definition starts
NOTE Confidence: 0.945285241666667
00:37:00.046 --> 00:37:03.510 with these different gradients,
NOTE Confidence: 0.945285241666667
00:37:03.510 --> 00:37:06.310 first identified by Denis O'Leary
NOTE Confidence: 0.945285241666667
00:37:06.310 --> 00:37:07.990 and his group,
NOTE Confidence: 0.945285241666667
00:37:07.990 --> 00:37:10.657 that you get a gradient of different
NOTE Confidence: 0.945285241666667
00:37:10.657 --> 00:37:12.845 factors that turn on different
NOTE Confidence: 0.945285241666667
00:37:12.845 --> 00:37:15.265 transcription factors in the brain,
NOTE Confidence: 0.945285241666667
00:37:15.270 --> 00:37:18.721 and it's the overlap of these different
NOTE Confidence: 0.945285241666667
00:37:18.721 --> 00:37:21.210 patterns of these signaling molecules.
NOTE Confidence: 0.945285241666667
00:37:21.210 --> 00:37:23.710 Turning on transcription factors that
NOTE Confidence: 0.945285241666667
00:37:23.710 --> 00:37:26.786 define these different regions of the brain,
NOTE Confidence: 0.945285241666667
00:37:26.790 --> 00:37:27.023 well,
NOTE Confidence: 0.945285241666667
00:37:27.023 --> 00:37:28.654 we had not actually been able to
NOTE Confidence: 0.945285241666667

00:37:28.654 --> 00:37:30.270 find any transcription factors.
NOTE Confidence: 0.945285241666667

00:37:30.270 --> 00:37:32.028 So we took a new approach,
NOTE Confidence: 0.945285241666667

00:37:32.030 --> 00:37:33.682 something called Samoa which
NOTE Confidence: 0.945285241666667

00:37:33.682 --> 00:37:35.747 stands for single molecule assay.
NOTE Confidence: 0.945285241666667

00:37:35.750 --> 00:37:38.529 And this is a highly sensitive methodology
NOTE Confidence: 0.945285241666667

00:37:38.529 --> 00:37:41.975 to be able to look at a single
NOTE Confidence: 0.945285241666667

00:37:41.975 --> 00:37:44.150 molecules interacting with each other.
NOTE Confidence: 0.945285241666667

00:37:44.150 --> 00:37:46.292 And we had to build a transcription
NOTE Confidence: 0.945285241666667

00:37:46.292 --> 00:37:47.830 factor library because one didn't
NOTE Confidence: 0.945285241666667

00:37:47.830 --> 00:37:49.225 exist for just the brains,
NOTE Confidence: 0.945285241666667

00:37:49.230 --> 00:37:51.490 we took all we actually.
NOTE Confidence: 0.945285241666667

00:37:51.490 --> 00:37:53.352 We cloned into a library all the
NOTE Confidence: 0.945285241666667

00:37:53.352 --> 00:37:54.431 transcription factors that are
NOTE Confidence: 0.945285241666667

00:37:54.431 --> 00:37:56.516 expressed in the brain and we then
NOTE Confidence: 0.945285241666667

00:37:56.516 --> 00:37:58.808 asked which ones interact with ARX.
NOTE Confidence: 0.945285241666667

00:37:58.810 --> 00:37:59.970 And when we did that

NOTE Confidence: 0.9469625333333333
00:38:02.410 --> 00:38:04.738 we were able to find a number of
NOTE Confidence: 0.9469625333333333
00:38:04.738 --> 00:38:06.690 different factor transcription factors.
NOTE Confidence: 0.9469625333333333
00:38:06.690 --> 00:38:08.334 Now that interacted with arx and
NOTE Confidence: 0.9469625333333333
00:38:08.334 --> 00:38:10.372 you can see they have overlapping
NOTE Confidence: 0.9469625333333333
00:38:10.372 --> 00:38:12.128 patterns in different regions,
NOTE Confidence: 0.9469625333333333
00:38:12.130 --> 00:38:14.650 so some just in the cortex,
NOTE Confidence: 0.9469625333333333
00:38:14.650 --> 00:38:17.536 others just in the ganglionic eminence.
NOTE Confidence: 0.9469625333333333
00:38:17.540 --> 00:38:18.914 And others that are both in
NOTE Confidence: 0.9469625333333333
00:38:18.914 --> 00:38:20.304 the cortex and the ganglionic
NOTE Confidence: 0.9469625333333333
00:38:20.304 --> 00:38:21.980 eminence in different patterns.
NOTE Confidence: 0.9469625333333333
00:38:21.980 --> 00:38:24.311 So this one just like ARX stronger
NOTE Confidence: 0.9469625333333333
00:38:24.311 --> 00:38:26.540 in the more posterior brain,
NOTE Confidence: 0.9469625333333333
00:38:26.540 --> 00:38:29.140 less so in the anterior.
NOTE Confidence: 0.9469625333333333
00:38:29.140 --> 00:38:31.820 And when we take and look at these
NOTE Confidence: 0.9469625333333333
00:38:31.820 --> 00:38:33.020 different transcription factors,
NOTE Confidence: 0.9469625333333333

00:38:33.020 --> 00:38:34.777 what we see is that the patterning,
NOTE Confidence: 0.9469625333333333

00:38:34.780 --> 00:38:37.012 the gene expression that define these
NOTE Confidence: 0.9469625333333333

00:38:37.012 --> 00:38:39.700 different regions in the brain is disrupted.
NOTE Confidence: 0.9469625333333333

00:38:39.700 --> 00:38:42.822 So you can see here in the
NOTE Confidence: 0.9469625333333333

00:38:42.822 --> 00:38:45.158 ARX and it's a a loss.
NOTE Confidence: 0.9469625333333333

00:38:45.158 --> 00:38:48.386 Of your frontal cortex and a
NOTE Confidence: 0.9469625333333333

00:38:48.386 --> 00:38:51.699 expansion of the ventral cortex.
NOTE Confidence: 0.9469625333333333

00:38:51.700 --> 00:38:56.576 When we lose a RX and to try and then map,
NOTE Confidence: 0.9469625333333333

00:38:56.580 --> 00:38:58.659 but we want to try and map,
NOTE Confidence: 0.9469625333333333

00:38:58.660 --> 00:38:59.360 well, OK,
NOTE Confidence: 0.9469625333333333

00:38:59.360 --> 00:39:01.110 these these these regions are
NOTE Confidence: 0.9469625333333333

00:39:01.110 --> 00:39:03.420 abnormal and the behaviors abnormal.
NOTE Confidence: 0.9469625333333333

00:39:03.420 --> 00:39:05.100 Can we connect those two?
NOTE Confidence: 0.9469625333333333

00:39:05.100 --> 00:39:07.500 So we wanted to look at the actual
NOTE Confidence: 0.9469625333333333

00:39:07.500 --> 00:39:08.915 Axon trajectories from these
NOTE Confidence: 0.9469625333333333

00:39:08.915 --> 00:39:10.415 different regions to strike,

NOTE Confidence: 0.9469625333333333
00:39:10.420 --> 00:39:12.690 start mapping that out and
NOTE Confidence: 0.9469625333333333
00:39:12.690 --> 00:39:15.890 so we can go into a mouse.
NOTE Confidence: 0.9469625333333333
00:39:15.890 --> 00:39:17.954 And we can actually inject these
NOTE Confidence: 0.9469625333333333
00:39:17.954 --> 00:39:19.716 different tracers that go along
NOTE Confidence: 0.9469625333333333
00:39:19.716 --> 00:39:21.648 axons are ones that cross axons.
NOTE Confidence: 0.9469625333333333
00:39:21.650 --> 00:39:23.290 And when we do that,
NOTE Confidence: 0.9469625333333333
00:39:23.290 --> 00:39:24.730 what you can see here in the sensory,
NOTE Confidence: 0.9469625333333333
00:39:24.730 --> 00:39:26.490 so this is Ventrilateral,
NOTE Confidence: 0.9469625333333333
00:39:26.490 --> 00:39:28.250 this is ventral posterior.
NOTE Confidence: 0.9469625333333333
00:39:28.250 --> 00:39:31.379 You can see the normal mapping of
NOTE Confidence: 0.9469625333333333
00:39:31.379 --> 00:39:33.946 the ventral lateral from the brain.
NOTE Confidence: 0.9469625333333333
00:39:33.946 --> 00:39:36.682 But here the ventral posterior despite
NOTE Confidence: 0.9469625333333333
00:39:36.682 --> 00:39:38.822 you having normal axons coming
NOTE Confidence: 0.9469625333333333
00:39:38.822 --> 00:39:40.366 through the internal commissure,
NOTE Confidence: 0.9469625333333333
00:39:40.370 --> 00:39:42.066 sorry, the internal capsule.
NOTE Confidence: 0.9469625333333333

00:39:42.066 --> 00:39:44.610 They don't go to ventral posterior.
NOTE Confidence: 0.9469625333333333

00:39:44.610 --> 00:39:47.193 So we can show very specific mapping
NOTE Confidence: 0.9469625333333333

00:39:47.193 --> 00:39:49.271 abnormalities and then correlate those
NOTE Confidence: 0.9469625333333333

00:39:49.271 --> 00:39:51.075 with these behavioral abnormalities
NOTE Confidence: 0.9469625333333333

00:39:51.075 --> 00:39:53.569 that we're seeing in the brain.
NOTE Confidence: 0.9469625333333333

00:39:53.570 --> 00:39:56.618 So we're going everywhere from the
NOTE Confidence: 0.9469625333333333

00:39:56.618 --> 00:39:58.466 molecular understanding of how the
NOTE Confidence: 0.9469625333333333

00:39:58.466 --> 00:40:00.899 cortex is defined to how that sets
NOTE Confidence: 0.9469625333333333

00:40:00.899 --> 00:40:02.694 up projections and connections and
NOTE Confidence: 0.9469625333333333

00:40:02.694 --> 00:40:04.768 what that does for the behavior
NOTE Confidence: 0.9469625333333333

00:40:04.768 --> 00:40:07.048 of the brain giving us a really a
NOTE Confidence: 0.9469625333333333

00:40:07.050 --> 00:40:10.260 view from behavior to the molecule.
NOTE Confidence: 0.9469625333333333

00:40:10.260 --> 00:40:12.990 In the brain and in these developmental
NOTE Confidence: 0.9469625333333333

00:40:12.990 --> 00:40:13.380 disorders.
NOTE Confidence: 0.947441742857143

00:40:16.100 --> 00:40:17.857 So that's some ongoing work we're doing.
NOTE Confidence: 0.947441742857143

00:40:17.860 --> 00:40:20.947 And and now I want to shift a little

NOTE Confidence: 0.947441742857143

00:40:20.947 --> 00:40:23.779 bit in the last 15 minutes or so

NOTE Confidence: 0.947441742857143

00:40:23.780 --> 00:40:26.012 and talk about some other relatively

NOTE Confidence: 0.947441742857143

00:40:26.012 --> 00:40:28.416 new work we've been doing and that

NOTE Confidence: 0.947441742857143

00:40:28.416 --> 00:40:31.340 is related to these two brains.

NOTE Confidence: 0.947441742857143

00:40:31.340 --> 00:40:34.460 So I already told you about this or

NOTE Confidence: 0.947441742857143

00:40:34.460 --> 00:40:37.811 showed you the brain of the ARX with an

NOTE Confidence: 0.947441742857143

00:40:37.811 --> 00:40:39.750 alanine tract expansion where you have an.

NOTE Confidence: 0.947441742857143

00:40:39.750 --> 00:40:43.278 A structurally normal brain, but with

NOTE Confidence: 0.947441742857143

00:40:43.278 --> 00:40:45.630 epilepsy and intellectual disabilities.

NOTE Confidence: 0.947441742857143

00:40:45.630 --> 00:40:50.256 Now these two kids also have epilepsy,

NOTE Confidence: 0.947441742857143

00:40:50.256 --> 00:40:52.494 mild intellectual disabilities,

NOTE Confidence: 0.947441742857143

00:40:52.494 --> 00:40:56.224 but a structurally normal brain.

NOTE Confidence: 0.947441742857143

00:40:56.230 --> 00:40:58.106 Now there may be some signal abnormality.

NOTE Confidence: 0.947441742857143

00:40:58.110 --> 00:41:00.070 You can see a little bit of brightness

NOTE Confidence: 0.947441742857143

00:41:00.070 --> 00:41:01.947 here in the thalamus and in the

NOTE Confidence: 0.947441742857143

00:41:01.947 --> 00:41:03.550 basal ganglia here in this one.
NOTE Confidence: 0.947441742857143

00:41:03.550 --> 00:41:05.748 And and that's typical of these disorders.
NOTE Confidence: 0.947441742857143

00:41:05.750 --> 00:41:09.758 These are due to mitochondrial disorders.
NOTE Confidence: 0.947441742857143

00:41:09.760 --> 00:41:11.895 So these are mitochondrial related
NOTE Confidence: 0.947441742857143

00:41:11.895 --> 00:41:14.402 epilepsies and these have always been
NOTE Confidence: 0.947441742857143

00:41:14.402 --> 00:41:16.802 thought to be due to a energy problem
NOTE Confidence: 0.947441742857143

00:41:16.802 --> 00:41:19.274 that the the might be neurons require
NOTE Confidence: 0.947441742857143

00:41:19.274 --> 00:41:21.571 a tremendous amount of of energy and
NOTE Confidence: 0.947441742857143

00:41:21.571 --> 00:41:23.353 you just have an energy deficiency.
NOTE Confidence: 0.947441742857143

00:41:23.360 --> 00:41:24.680 If we could replace that,
NOTE Confidence: 0.947441742857143

00:41:24.680 --> 00:41:26.675 we'd be able to fix their epilepsy.
NOTE Confidence: 0.947441742857143

00:41:26.680 --> 00:41:28.423 Turns out it hasn't been that simple
NOTE Confidence: 0.947441742857143

00:41:28.423 --> 00:41:30.479 and it it doesn't work that well.
NOTE Confidence: 0.947441742857143

00:41:30.480 --> 00:41:31.800 So we we started thinking,
NOTE Confidence: 0.947441742857143

00:41:31.800 --> 00:41:32.572 you know,
NOTE Confidence: 0.947441742857143

00:41:32.572 --> 00:41:34.888 maybe it's more complicated than that.

NOTE Confidence: 0.947441742857143

00:41:34.890 --> 00:41:37.018 And so we first looked at the

NOTE Confidence: 0.947441742857143

00:41:37.018 --> 00:41:39.475 literature and it turns out that a

NOTE Confidence: 0.947441742857143

00:41:39.475 --> 00:41:41.320 significant percentage of kids that

NOTE Confidence: 0.947441742857143

00:41:41.320 --> 00:41:43.523 have mitochondrial disorders have

NOTE Confidence: 0.947441742857143

00:41:43.523 --> 00:41:48.570 either abnormal Eegs or frank epilepsy.

NOTE Confidence: 0.947441742857143

00:41:48.570 --> 00:41:51.895 And so we started studying this and

NOTE Confidence: 0.947441742857143

00:41:51.895 --> 00:41:53.890 we looked at both the excitatory and

NOTE Confidence: 0.947441742857143

00:41:53.890 --> 00:41:55.768 inhibitory neurons because our prediction is,

NOTE Confidence: 0.947441742857143

00:41:55.770 --> 00:41:57.774 remember the inhibitory when you have

NOTE Confidence: 0.947441742857143

00:41:57.774 --> 00:42:00.369 a defect in the excitatory neurons,

NOTE Confidence: 0.947441742857143

00:42:00.370 --> 00:42:01.610 the brains are structurally normal,

NOTE Confidence: 0.947441742857143

00:42:01.610 --> 00:42:04.928 but with inhibitory neurons you get a.

NOTE Confidence: 0.947441742857143

00:42:04.930 --> 00:42:07.506 Seizures and intellectual disabilities.

NOTE Confidence: 0.947441742857143

00:42:07.506 --> 00:42:12.112 So on the left side we've labeled

NOTE Confidence: 0.947441742857143

00:42:12.112 --> 00:42:15.567 migrating excitatory neurons in green,

NOTE Confidence: 0.947441742857143

00:42:15.570 --> 00:42:18.210 and then in red we've labeled
NOTE Confidence: 0.947441742857143

00:42:18.210 --> 00:42:19.090 their mitochondria.
NOTE Confidence: 0.947441742857143

00:42:19.090 --> 00:42:21.498 And what you can see is it migrates
NOTE Confidence: 0.947441742857143

00:42:21.498 --> 00:42:23.226 across is that the mitochondria
NOTE Confidence: 0.947441742857143

00:42:23.226 --> 00:42:25.836 stay just in front of the cell body
NOTE Confidence: 0.947441742857143

00:42:25.836 --> 00:42:27.607 as it migrates all the way across,
NOTE Confidence: 0.947441742857143

00:42:27.610 --> 00:42:28.602 and we've mapped that.
NOTE Confidence: 0.947441742857143

00:42:28.602 --> 00:42:31.300 At the top you can see a quantitation
NOTE Confidence: 0.947441742857143

00:42:31.300 --> 00:42:32.510 of that.
NOTE Confidence: 0.947441742857143

00:42:32.510 --> 00:42:33.750 But if you look at the of the,
NOTE Confidence: 0.947441742857143

00:42:33.750 --> 00:42:34.054 sorry,
NOTE Confidence: 0.947441742857143

00:42:34.054 --> 00:42:36.486 the one on the right that's in a
NOTE Confidence: 0.947441742857143

00:42:36.486 --> 00:42:38.262 migrating inhibitory neuron and
NOTE Confidence: 0.947441742857143

00:42:38.262 --> 00:42:39.670 the mitochondria behave very
NOTE Confidence: 0.947441742857143

00:42:39.670 --> 00:42:41.430 differently in all of them.
NOTE Confidence: 0.947441742857143

00:42:41.430 --> 00:42:42.220 Inhibitory neurons,

NOTE Confidence: 0.947441742857143
00:42:42.220 --> 00:42:44.590 they move around through the cells.
NOTE Confidence: 0.947441742857143
00:42:44.590 --> 00:42:45.570 Sometimes they go up
NOTE Confidence: 0.947441742857143
00:42:45.570 --> 00:42:46.550 into the leading process,
NOTE Confidence: 0.947441742857143
00:42:46.550 --> 00:42:48.126 particularly at branch points,
NOTE Confidence: 0.947441742857143
00:42:48.126 --> 00:42:50.490 sometimes they're behind the cell body
NOTE Confidence: 0.947441742857143
00:42:50.554 --> 00:42:52.668 and sometimes they're in front of it.
NOTE Confidence: 0.947441742857143
00:42:52.670 --> 00:42:53.270 So there's this
NOTE Confidence: 0.95434236
00:42:55.910 --> 00:42:57.705 tremendous dynamic movement in the
NOTE Confidence: 0.95434236
00:42:57.705 --> 00:42:59.500 inhibitory neurons that you don't
NOTE Confidence: 0.95434236
00:42:59.562 --> 00:43:01.147 see in the excitatory neurons.
NOTE Confidence: 0.95434236
00:43:01.150 --> 00:43:03.070 And so to study this further,
NOTE Confidence: 0.95434236
00:43:03.070 --> 00:43:04.670 so this is just observation,
NOTE Confidence: 0.95434236
00:43:04.670 --> 00:43:06.790 we actually started to interrogate
NOTE Confidence: 0.95434236
00:43:06.790 --> 00:43:09.335 that we used a genetic model
NOTE Confidence: 0.95434236
00:43:09.335 --> 00:43:12.170 where we removed this Ant 1-2,
NOTE Confidence: 0.95434236

00:43:12.170 --> 00:43:15.830 this is a transporter of a TP.
NOTE Confidence: 0.95434236

00:43:15.830 --> 00:43:17.930 We also did it pharmacologically
NOTE Confidence: 0.95434236

00:43:17.930 --> 00:43:19.190 using boncretic acid,
NOTE Confidence: 0.95434236

00:43:19.190 --> 00:43:21.605 which actually is an inhibitor of this
NOTE Confidence: 0.95434236

00:43:21.605 --> 00:43:23.526 transporter or we used oligomycin,
NOTE Confidence: 0.95434236

00:43:23.526 --> 00:43:26.527 which is an inhibitor of the last
NOTE Confidence: 0.95434236

00:43:26.527 --> 00:43:29.297 step in the oxidative phosphorylation.
NOTE Confidence: 0.95434236

00:43:29.300 --> 00:43:30.540 And I will tell you,
NOTE Confidence: 0.95434236

00:43:30.540 --> 00:43:32.538 but I'm not going to show you any data
NOTE Confidence: 0.95434236

00:43:32.540 --> 00:43:34.815 to ensure that it wasn't just lycolysis.
NOTE Confidence: 0.95434236

00:43:34.820 --> 00:43:35.876 We blocked lycolysis.
NOTE Confidence: 0.95434236

00:43:35.876 --> 00:43:38.700 What we were able to show is that
NOTE Confidence: 0.95434236

00:43:38.700 --> 00:43:40.300 radial migration is completely
NOTE Confidence: 0.90250405

00:43:46.760 --> 00:43:48.304 whereas the inhibitory neuron
NOTE Confidence: 0.90250405

00:43:48.304 --> 00:43:50.234 is required for is requires
NOTE Confidence: 0.90250405

00:43:50.234 --> 00:43:51.600 oxidative phosphorylation.

NOTE Confidence: 0.90250405
00:43:51.600 --> 00:43:52.656 But I'm not going to talk
NOTE Confidence: 0.90250405
00:43:52.656 --> 00:43:53.360 about that part again,
NOTE Confidence: 0.90250405
00:43:53.360 --> 00:43:56.466 this has been published now if
NOTE Confidence: 0.90250405
00:43:56.466 --> 00:43:59.160 you look, let's see, let's.
NOTE Confidence: 0.944566485714286
00:44:01.240 --> 00:44:02.717 How come these movies are not playing?
NOTE Confidence: 0.91832676
00:44:06.640 --> 00:44:08.120 They were working a second ago. Okay,
NOTE Confidence: 0.914349101818182
00:44:11.320 --> 00:44:13.208 I'm not going to be able to show
NOTE Confidence: 0.914349101818182
00:44:13.208 --> 00:44:16.000 you these movies on your left is in
NOTE Confidence: 0.914349101818182
00:44:16.000 --> 00:44:19.030 in culture looking at inhibitory
NOTE Confidence: 0.914349101818182
00:44:19.030 --> 00:44:22.352 neurons and what you'd see is that
NOTE Confidence: 0.914349101818182
00:44:22.352 --> 00:44:25.537 that on the top, a normal one.
NOTE Confidence: 0.914349101818182
00:44:25.537 --> 00:44:27.832 These, these inhibitory neurons have
NOTE Confidence: 0.914349101818182
00:44:27.832 --> 00:44:29.859 tremendous branching as they migrate.
NOTE Confidence: 0.914349101818182
00:44:29.860 --> 00:44:32.058 And it it'll just kind of zoom
NOTE Confidence: 0.914349101818182
00:44:32.058 --> 00:44:34.290 across the the field at the bottom.
NOTE Confidence: 0.914349101818182

00:44:34.290 --> 00:44:36.696 What you'll see is that when you add
NOTE Confidence: 0.914349101818182

00:44:36.696 --> 00:44:39.208 oligomycin or when we do it with bancrecic
NOTE Confidence: 0.914349101818182

00:44:39.208 --> 00:44:41.379 acid or when we do it genetically,
NOTE Confidence: 0.914349101818182

00:44:41.380 --> 00:44:43.459 they don't just migrate across the field.
NOTE Confidence: 0.914349101818182

00:44:43.460 --> 00:44:45.924 They go forward and then you see a
NOTE Confidence: 0.914349101818182

00:44:45.924 --> 00:44:48.203 leading process coming out of the rear
NOTE Confidence: 0.914349101818182

00:44:48.203 --> 00:44:50.209 and the cell actually turning around
NOTE Confidence: 0.914349101818182

00:44:50.209 --> 00:44:52.243 and going backwards and going back
NOTE Confidence: 0.914349101818182

00:44:52.243 --> 00:44:54.168 and forth and not branching as much.
NOTE Confidence: 0.914349101818182

00:44:54.168 --> 00:44:56.111 And then if you look in the genetic
NOTE Confidence: 0.914349101818182

00:44:56.111 --> 00:44:57.707 model where we actually are looking
NOTE Confidence: 0.914349101818182

00:44:57.707 --> 00:44:59.229 at the cells migrating up,
NOTE Confidence: 0.914349101818182

00:44:59.230 --> 00:45:00.862 you'll see a defect in those
NOTE Confidence: 0.914349101818182

00:45:00.862 --> 00:45:02.629 cells going up into the cortex,
NOTE Confidence: 0.914349101818182

00:45:02.630 --> 00:45:06.068 these inhibitory neurons.
NOTE Confidence: 0.914349101818182

00:45:06.070 --> 00:45:10.590 What what we found is that when we do this,

NOTE Confidence: 0.914349101818182
00:45:10.590 --> 00:45:12.830 we. So why do cells turn around?
NOTE Confidence: 0.914349101818182
00:45:12.830 --> 00:45:14.380 It turns out all epithelial
NOTE Confidence: 0.914349101818182
00:45:14.380 --> 00:45:15.631 cells are polarized, right?
NOTE Confidence: 0.914349101818182
00:45:15.631 --> 00:45:16.594 And they're polarized.
NOTE Confidence: 0.914349101818182
00:45:16.594 --> 00:45:19.228 You have the nucleus and then you have the
NOTE Confidence: 0.914349101818182
00:45:19.230 --> 00:45:21.830 MTOC, the microtubule organizing center.
NOTE Confidence: 0.914349101818182
00:45:21.830 --> 00:45:23.228 It's also known as the centriole.
NOTE Confidence: 0.914349101818182
00:45:23.230 --> 00:45:24.030 In the dividing cell,
NOTE Confidence: 0.914349101818182
00:45:24.030 --> 00:45:24.830 it's the same thing.
NOTE Confidence: 0.914349101818182
00:45:24.830 --> 00:45:26.546 It's where the microtubules are organized
NOTE Confidence: 0.914320166
00:45:29.030 --> 00:45:31.706 as cells migrate that that MTOC moves
NOTE Confidence: 0.914320166
00:45:31.706 --> 00:45:33.512 out into the leading process and then
NOTE Confidence: 0.914320166
00:45:33.512 --> 00:45:35.306 the nucleus gets pulled behind it.
NOTE Confidence: 0.914320166
00:45:35.310 --> 00:45:37.390 That's how they migrate out.
NOTE Confidence: 0.914320166
00:45:37.390 --> 00:45:38.758 But in these cells,
NOTE Confidence: 0.914320166

00:45:38.758 --> 00:45:40.468 when you lose the mitochondria,
NOTE Confidence: 0.914320166

00:45:40.470 --> 00:45:42.094 you lose that polarization.
NOTE Confidence: 0.914320166

00:45:42.094 --> 00:45:44.530 And both in the genetic model
NOTE Confidence: 0.914320166

00:45:44.601 --> 00:45:46.876 and in the pharmacologic models.
NOTE Confidence: 0.914320166

00:45:46.880 --> 00:45:49.280 The mitochondria, sorry, the MTOC,
NOTE Confidence: 0.914320166

00:45:49.280 --> 00:45:51.160 is found over the top of the nucleus
NOTE Confidence: 0.914320166

00:45:51.160 --> 00:45:52.837 or sometimes even behind the nucleus,
NOTE Confidence: 0.914320166

00:45:52.840 --> 00:45:54.015 and that's when those cells
NOTE Confidence: 0.914320166

00:45:54.015 --> 00:45:54.720 are turning around.
NOTE Confidence: 0.914320166

00:45:54.720 --> 00:45:57.751 So you're losing the polar polarity that
NOTE Confidence: 0.914320166

00:45:57.751 --> 00:46:00.639 a normal epithelial cell in a neuron has.
NOTE Confidence: 0.914320166

00:46:00.640 --> 00:46:04.600 And that's what we have found
NOTE Confidence: 0.914320166

00:46:04.600 --> 00:46:06.268 so more recently,
NOTE Confidence: 0.914320166

00:46:06.268 --> 00:46:10.160 and that that works all been published.
NOTE Confidence: 0.914320166

00:46:10.160 --> 00:46:11.946 So more recently we started asking, well,
NOTE Confidence: 0.914320166

00:46:11.946 --> 00:46:14.268 mitochondria move through the cell, why?

NOTE Confidence: 0.914320166

00:46:14.268 --> 00:46:16.984 Why are they moving in inhibitory neurons?

NOTE Confidence: 0.914320166

00:46:16.990 --> 00:46:19.636 And it turns out that mitochondria are

NOTE Confidence: 0.914320166

00:46:19.636 --> 00:46:21.989 moved along using molecular motors,

NOTE Confidence: 0.914320166

00:46:21.990 --> 00:46:24.549 moved along microtubules.

NOTE Confidence: 0.914320166

00:46:24.550 --> 00:46:26.950 And so we started thinking about,

NOTE Confidence: 0.914320166

00:46:26.950 --> 00:46:27.634 you know,

NOTE Confidence: 0.914320166

00:46:27.634 --> 00:46:29.782 how could we disrupt that and

NOTE Confidence: 0.914320166

00:46:29.782 --> 00:46:32.006 the way that the mitochondria

NOTE Confidence: 0.914320166

00:46:32.006 --> 00:46:33.990 attached these molecular motors,

NOTE Confidence: 0.914320166

00:46:33.990 --> 00:46:36.684 because dyneins and kinesins move many

NOTE Confidence: 0.914320166

00:46:36.684 --> 00:46:39.190 types of cargo throughout the cell,

NOTE Confidence: 0.914320166

00:46:39.190 --> 00:46:41.386 putting things that like Polybee studying,

NOTE Confidence: 0.914320166

00:46:41.390 --> 00:46:43.958 but the they they attached to

NOTE Confidence: 0.914320166

00:46:43.958 --> 00:46:45.670 the mitochondria using these.

NOTE Confidence: 0.914320166

00:46:45.670 --> 00:46:46.470 Adapter proteins,

NOTE Confidence: 0.914320166

00:46:46.470 --> 00:46:49.270 which are called mirror one and mirror
NOTE Confidence: 0.914320166

00:46:49.270 --> 00:46:52.070 two and there's another one called track,
NOTE Confidence: 0.914320166

00:46:52.070 --> 00:46:53.906 Now mirror one and mirror two,
NOTE Confidence: 0.914320166

00:46:53.910 --> 00:46:55.686 sorry, mirror two is almost not
NOTE Confidence: 0.914320166

00:46:55.686 --> 00:46:57.230 expressed in the developing brain.
NOTE Confidence: 0.914320166

00:46:57.230 --> 00:46:59.785 So we just focused on mirror one.
NOTE Confidence: 0.914320166

00:46:59.790 --> 00:47:02.790 And so mirror one's the main adapter protein.
NOTE Confidence: 0.914320166

00:47:02.790 --> 00:47:05.230 And if we take a knockout mirror one,
NOTE Confidence: 0.914320166

00:47:05.230 --> 00:47:07.378 what you see is hearing in
NOTE Confidence: 0.914320166

00:47:07.378 --> 00:47:09.630 normal mice in radial migration,
NOTE Confidence: 0.914320166

00:47:09.630 --> 00:47:12.340 you can see that the.
NOTE Confidence: 0.914320166

00:47:12.340 --> 00:47:13.492 Mitochondria are always out
NOTE Confidence: 0.914320166

00:47:13.492 --> 00:47:14.932 at the front of that,
NOTE Confidence: 0.914320166

00:47:14.940 --> 00:47:16.578 just like I showed you before,
NOTE Confidence: 0.914320166

00:47:16.580 --> 00:47:17.876 are always out at the front
NOTE Confidence: 0.914320166

00:47:17.876 --> 00:47:18.740 of the leading process.

NOTE Confidence: 0.914320166
00:47:18.740 --> 00:47:21.140 These cells are migrating up.
NOTE Confidence: 0.914320166
00:47:21.140 --> 00:47:23.280 If you look at the when
NOTE Confidence: 0.914320166
00:47:23.280 --> 00:47:24.980 we knock out mirror one,
NOTE Confidence: 0.914320166
00:47:24.980 --> 00:47:27.284 most of the time the mirror ones at
NOTE Confidence: 0.914320166
00:47:27.284 --> 00:47:29.833 the back of the nucleus and again
NOTE Confidence: 0.914320166
00:47:29.833 --> 00:47:31.733 these cells migrate out normally.
NOTE Confidence: 0.914320166
00:47:31.740 --> 00:47:33.498 So it's not affecting their migration,
NOTE Confidence: 0.914320166
00:47:33.500 --> 00:47:35.275 it's just affecting the localization
NOTE Confidence: 0.914320166
00:47:35.275 --> 00:47:36.340 of the mitochondria.
NOTE Confidence: 0.914320166
00:47:36.340 --> 00:47:38.340 Sometimes it's even in front and in back,
NOTE Confidence: 0.914320166
00:47:38.340 --> 00:47:41.328 like you see here and here.
NOTE Confidence: 0.914320166
00:47:41.330 --> 00:47:42.066 In contrast,
NOTE Confidence: 0.914320166
00:47:42.066 --> 00:47:44.642 when we look at the inhibitory neurons,
NOTE Confidence: 0.914320166
00:47:44.650 --> 00:47:46.421 we see that the the the mitochondria
NOTE Confidence: 0.914320166
00:47:46.421 --> 00:47:48.124 all of a sudden just aggregate
NOTE Confidence: 0.914320166

00:47:48.124 --> 00:47:49.888 at the front of the cell.
NOTE Confidence: 0.914320166

00:47:49.890 --> 00:47:51.846 So we do something called expansion
NOTE Confidence: 0.914320166

00:47:51.846 --> 00:47:53.498 microscopy where we can actually
NOTE Confidence: 0.914320166

00:47:53.498 --> 00:47:55.528 get a better look at these cells.
NOTE Confidence: 0.914320166

00:47:55.530 --> 00:47:57.228 Looking at the mitochondria we see
NOTE Confidence: 0.914320166

00:47:57.228 --> 00:47:59.890 not only is are they they stuck,
NOTE Confidence: 0.914320166

00:47:59.890 --> 00:48:02.370 but they're also abnormal.
NOTE Confidence: 0.914320166

00:48:02.370 --> 00:48:04.536 They become very small and punctate
NOTE Confidence: 0.914320166

00:48:04.536 --> 00:48:06.865 as opposed to being nice and
NOTE Confidence: 0.914320166

00:48:06.865 --> 00:48:08.485 long and sometimes branched.
NOTE Confidence: 0.914320166

00:48:08.490 --> 00:48:09.898 As you see here,
NOTE Confidence: 0.914320166

00:48:09.898 --> 00:48:12.650 so this is the defects that we see.
NOTE Confidence: 0.914320166

00:48:12.650 --> 00:48:14.870 And we also see the same
NOTE Confidence: 0.914320166

00:48:14.870 --> 00:48:15.610 polarization defects.
NOTE Confidence: 0.914320166

00:48:15.610 --> 00:48:17.283 So we can look at the direction
NOTE Confidence: 0.914320166

00:48:17.283 --> 00:48:18.831 these cells are migrating and we

NOTE Confidence: 0.914320166

00:48:18.831 --> 00:48:20.644 this is just how we calculated it.

NOTE Confidence: 0.914320166

00:48:20.650 --> 00:48:22.570 Oh, whoops.

NOTE Confidence: 0.914320166

00:48:22.570 --> 00:48:24.970 Oh, I must have, sorry I took out a slide.

NOTE Confidence: 0.914320166

00:48:24.970 --> 00:48:26.850 But when we quantitate this,

NOTE Confidence: 0.914320166

00:48:26.850 --> 00:48:28.272 you can see that there's a

NOTE Confidence: 0.914320166

00:48:28.272 --> 00:48:29.220 huge number of cells

NOTE Confidence: 0.940812677777778

00:48:29.276 --> 00:48:30.902 that are going in the wrong

NOTE Confidence: 0.940812677777778

00:48:30.902 --> 00:48:32.374 direction here. They're all supposed

NOTE Confidence: 0.940812677777778

00:48:32.374 --> 00:48:34.210 to be going north up this way.

NOTE Confidence: 0.935245477142857

00:48:36.680 --> 00:48:38.790 And these mice are also

NOTE Confidence: 0.935245477142857

00:48:38.790 --> 00:48:39.634 behaviorally abnormal.

NOTE Confidence: 0.935245477142857

00:48:39.640 --> 00:48:40.792 So normally mice,

NOTE Confidence: 0.935245477142857

00:48:40.792 --> 00:48:43.096 if you put these little white

NOTE Confidence: 0.935245477142857

00:48:43.096 --> 00:48:45.560 pads like this one you see here,

NOTE Confidence: 0.935245477142857

00:48:45.560 --> 00:48:47.839 they build a nest out of it and

NOTE Confidence: 0.935245477142857

00:48:47.839 --> 00:48:49.792 you can see the wild type mouse
NOTE Confidence: 0.935245477142857

00:48:49.792 --> 00:48:51.450 over there building this nice
NOTE Confidence: 0.935245477142857

00:48:51.450 --> 00:48:53.514 normal round nest that they use.
NOTE Confidence: 0.935245477142857

00:48:53.520 --> 00:48:55.356 But if you look at these
NOTE Confidence: 0.935245477142857

00:48:55.356 --> 00:48:56.274 marijuana knockout mice,
NOTE Confidence: 0.935245477142857

00:48:56.280 --> 00:48:58.400 they they don't build a nest at all.
NOTE Confidence: 0.935245477142857

00:48:58.400 --> 00:49:00.598 You can see some don't do anything,
NOTE Confidence: 0.935245477142857

00:49:00.600 --> 00:49:01.755 some tear it up a little bit,
NOTE Confidence: 0.935245477142857

00:49:01.760 --> 00:49:03.237 some tear it up a little more,
NOTE Confidence: 0.935245477142857

00:49:03.240 --> 00:49:05.865 but they don't make an organized nest.
NOTE Confidence: 0.935245477142857

00:49:05.870 --> 00:49:09.410 They also have a interesting
NOTE Confidence: 0.935245477142857

00:49:09.410 --> 00:49:11.344 behavioral phenotype where
NOTE Confidence: 0.935245477142857

00:49:11.344 --> 00:49:14.428 they they have a high anxiety.
NOTE Confidence: 0.935245477142857

00:49:14.430 --> 00:49:17.374 So the way you test anxiety in the
NOTE Confidence: 0.935245477142857

00:49:17.374 --> 00:49:20.354 mouse is that normally a mouse if you
NOTE Confidence: 0.935245477142857

00:49:20.354 --> 00:49:23.940 put it into a open field they're they

NOTE Confidence: 0.935245477142857
00:49:23.940 --> 00:49:27.068 they'll explore the entire box okay.
NOTE Confidence: 0.935245477142857
00:49:27.068 --> 00:49:30.416 But if you if they have.
NOTE Confidence: 0.935245477142857
00:49:30.420 --> 00:49:32.202 What's thought to be anxiety and
NOTE Confidence: 0.935245477142857
00:49:32.202 --> 00:49:33.524 again you know, anthropomorphosizing.
NOTE Confidence: 0.935245477142857
00:49:33.524 --> 00:49:35.220 What a mouse does,
NOTE Confidence: 0.935245477142857
00:49:35.220 --> 00:49:36.860 if it has high anxiety,
NOTE Confidence: 0.935245477142857
00:49:36.860 --> 00:49:39.220 they will tend to stay outside of the
NOTE Confidence: 0.935245477142857
00:49:39.220 --> 00:49:41.660 center and stay at the edges of the box.
NOTE Confidence: 0.935245477142857
00:49:41.660 --> 00:49:43.304 And here's what our mice with
NOTE Confidence: 0.935245477142857
00:49:43.304 --> 00:49:44.700 mirror one mutations look like.
NOTE Confidence: 0.935245477142857
00:49:44.700 --> 00:49:47.787 They stay at the outside of the box as
NOTE Confidence: 0.935245477142857
00:49:47.787 --> 00:49:50.819 opposed to exploring the middle of the box.
NOTE Confidence: 0.935245477142857
00:49:50.820 --> 00:49:52.650 The other thing that's quite interesting
NOTE Confidence: 0.935245477142857
00:49:52.650 --> 00:49:55.311 is if you look at a mouse in what's
NOTE Confidence: 0.935245477142857
00:49:55.311 --> 00:49:56.696 called an elevated plus maze,
NOTE Confidence: 0.935245477142857

00:49:56.700 --> 00:49:58.708 and this is a little more than an
NOTE Confidence: 0.935245477142857

00:49:58.708 --> 00:50:00.179 elevated plus maze because the.
NOTE Confidence: 0.935245477142857

00:50:00.180 --> 00:50:03.568 The arms that go up and down
NOTE Confidence: 0.935245477142857

00:50:03.568 --> 00:50:05.033 are actually enclosed,
NOTE Confidence: 0.935245477142857

00:50:05.033 --> 00:50:08.977 whereas the ones that go sideways are open.
NOTE Confidence: 0.935245477142857

00:50:08.980 --> 00:50:09.484 And once again,
NOTE Confidence: 0.935245477142857

00:50:09.484 --> 00:50:10.940 if you look at a wild type mouse,
NOTE Confidence: 0.935245477142857

00:50:10.940 --> 00:50:12.780 it'll explore all of those.
NOTE Confidence: 0.935245477142857

00:50:12.780 --> 00:50:14.016 But interestingly, these mice,
NOTE Confidence: 0.935245477142857

00:50:14.016 --> 00:50:16.579 and this is a little different than anxiety.
NOTE Confidence: 0.935245477142857

00:50:16.580 --> 00:50:19.500 This is thought to be kind of a
NOTE Confidence: 0.935245477142857

00:50:19.500 --> 00:50:21.020 claustrophobia type phenotype.
NOTE Confidence: 0.935245477142857

00:50:21.020 --> 00:50:22.802 You see that they don't enter
NOTE Confidence: 0.935245477142857

00:50:22.802 --> 00:50:24.300 that closed box at all,
NOTE Confidence: 0.935245477142857

00:50:24.300 --> 00:50:26.368 They're anxious about entering
NOTE Confidence: 0.935245477142857

00:50:26.368 --> 00:50:27.919 the closed arms.

NOTE Confidence: 0.935245477142857
00:50:27.920 --> 00:50:28.572 Of this,
NOTE Confidence: 0.935245477142857
00:50:28.572 --> 00:50:30.528 whereas the wild type go through
NOTE Confidence: 0.935245477142857
00:50:30.528 --> 00:50:32.879 all of the arms of these boxes.
NOTE Confidence: 0.935245477142857
00:50:32.880 --> 00:50:34.256 So again,
NOTE Confidence: 0.935245477142857
00:50:34.256 --> 00:50:39.204 these behavioral defects and we think
NOTE Confidence: 0.935245477142857
00:50:39.204 --> 00:50:41.314 the brains are structurally normal,
NOTE Confidence: 0.935245477142857
00:50:41.320 --> 00:50:43.090 the brains of the kids are
NOTE Confidence: 0.935245477142857
00:50:43.090 --> 00:50:43.680 structurally normal.
NOTE Confidence: 0.935245477142857
00:50:43.680 --> 00:50:46.000 They have these different
NOTE Confidence: 0.935245477142857
00:50:46.000 --> 00:50:47.160 behavioral phenotypes,
NOTE Confidence: 0.935245477142857
00:50:47.160 --> 00:50:49.680 they have epilepsy just like these mice do.
NOTE Confidence: 0.92769987
00:50:53.070 --> 00:50:54.806 And so we're now looking to see and
NOTE Confidence: 0.92769987
00:50:54.806 --> 00:50:56.673 and this is going to be the end of
NOTE Confidence: 0.92769987
00:50:56.673 --> 00:50:58.119 the story that we're looking to
NOTE Confidence: 0.92769987
00:50:58.119 --> 00:50:59.715 see what the connectivity is and
NOTE Confidence: 0.92769987

00:50:59.715 --> 00:51:02.430 what the changes in gene expression
NOTE Confidence: 0.92769987

00:51:02.430 --> 00:51:04.242 leading us to really think that
NOTE Confidence: 0.92769987

00:51:04.242 --> 00:51:06.026 this epilepsy phenotype that you
NOTE Confidence: 0.92769987

00:51:06.026 --> 00:51:07.871 have in the behavioral phenotype
NOTE Confidence: 0.92769987

00:51:07.871 --> 00:51:09.830 is not just an energy defect.
NOTE Confidence: 0.92769987

00:51:09.830 --> 00:51:12.050 It's actually a neurodevelopmental
NOTE Confidence: 0.92769987

00:51:12.050 --> 00:51:14.825 defect from these inhibitory neurons.
NOTE Confidence: 0.92769987

00:51:14.830 --> 00:51:16.030 And this is just a summation
NOTE Confidence: 0.92769987

00:51:16.030 --> 00:51:17.030 diagram where you see the,
NOTE Confidence: 0.958942771428571

00:51:19.790 --> 00:51:20.936 the excitatory neurons,
NOTE Confidence: 0.958942771428571

00:51:20.936 --> 00:51:22.464 they migrate out normally.
NOTE Confidence: 0.958942771428571

00:51:22.470 --> 00:51:24.318 We don't know that they function normally
NOTE Confidence: 0.958942771428571

00:51:24.318 --> 00:51:26.070 with the with without mirror one,
NOTE Confidence: 0.958942771428571

00:51:26.070 --> 00:51:27.568 but we know they migrate normally and
NOTE Confidence: 0.958942771428571

00:51:27.568 --> 00:51:29.388 they form a structurally normal brain.
NOTE Confidence: 0.958942771428571

00:51:29.390 --> 00:51:31.250 But in contrast, these inhibitory

NOTE Confidence: 0.958942771428571

00:51:31.250 --> 00:51:33.110 neurons don't migrate out normally.

NOTE Confidence: 0.958942771428571

00:51:33.110 --> 00:51:34.720 The mitochondria stay localized right

NOTE Confidence: 0.958942771428571

00:51:34.720 --> 00:51:37.006 at the front as opposed to distributing

NOTE Confidence: 0.958942771428571

00:51:37.006 --> 00:51:38.866 in different parts of the cell.

NOTE Confidence: 0.958942771428571

00:51:38.870 --> 00:51:41.372 And we actually have been able

NOTE Confidence: 0.958942771428571

00:51:41.372 --> 00:51:43.908 to show that this is due to

NOTE Confidence: 0.958942771428571

00:51:43.910 --> 00:51:46.310 the the the inhibitory neurons.

NOTE Confidence: 0.958942771428571

00:51:46.310 --> 00:51:47.682 They need mitochondria in

NOTE Confidence: 0.958942771428571

00:51:47.682 --> 00:51:49.397 the rear of the cell.

NOTE Confidence: 0.958942771428571

00:51:49.400 --> 00:51:53.075 Because they require a separate type of.

NOTE Confidence: 0.958942771428571

00:51:53.080 --> 00:51:55.000 It's kind of like thinking about

NOTE Confidence: 0.958942771428571

00:51:55.000 --> 00:51:56.899 squeezing a toothpaste at the back.

NOTE Confidence: 0.958942771428571

00:51:56.899 --> 00:51:59.090 They need that for their migration in

NOTE Confidence: 0.958942771428571

00:51:59.156 --> 00:52:01.599 addition to the pulling from the front,

NOTE Confidence: 0.958942771428571

00:52:01.600 --> 00:52:03.030 whereas the excitatory neurons don't

NOTE Confidence: 0.958942771428571

00:52:03.030 --> 00:52:05.320 seem to need that or as much of that.

NOTE Confidence: 0.92415216

00:52:07.480 --> 00:52:10.717 So let me end by just doing a

NOTE Confidence: 0.92415216

00:52:10.717 --> 00:52:12.312 brief summary and then thanking

NOTE Confidence: 0.92415216

00:52:12.312 --> 00:52:13.997 the people who did the work.

NOTE Confidence: 0.92415216

00:52:14.000 --> 00:52:15.565 Hopefully I've given you a

NOTE Confidence: 0.92415216

00:52:15.565 --> 00:52:17.546 little bit of insight into how

NOTE Confidence: 0.92415216

00:52:17.546 --> 00:52:19.316 inner neurons might be involved.

NOTE Confidence: 0.92415216

00:52:19.320 --> 00:52:20.592 In these different

NOTE Confidence: 0.92415216

00:52:20.592 --> 00:52:21.440 neurodevelopmental disabilities,

NOTE Confidence: 0.92415216

00:52:21.440 --> 00:52:24.072 by by being able to tease out the

NOTE Confidence: 0.92415216

00:52:24.072 --> 00:52:26.121 specific role of the inhibitory

NOTE Confidence: 0.92415216

00:52:26.121 --> 00:52:28.550 neurons in the epilepsy versus the

NOTE Confidence: 0.92415216

00:52:28.550 --> 00:52:30.540 structural defects and now even

NOTE Confidence: 0.92415216

00:52:30.614 --> 00:52:32.844 the behavioral defects and how

NOTE Confidence: 0.92415216

00:52:32.844 --> 00:52:35.074 that affects these different mice.

NOTE Confidence: 0.92415216

00:52:35.080 --> 00:52:37.754 We begin to get new insights in

NOTE Confidence: 0.917715220833333
00:52:43.680 --> 00:52:45.575 to how these different defects
NOTE Confidence: 0.917715220833333
00:52:45.575 --> 00:52:48.200 led to new studies in terms of.
NOTE Confidence: 0.917715220833333
00:52:48.200 --> 00:52:49.675 What, how you might be
NOTE Confidence: 0.917715220833333
00:52:49.675 --> 00:52:50.560 treating these patients.
NOTE Confidence: 0.917715220833333
00:52:50.560 --> 00:52:52.648 So for example through another set
NOTE Confidence: 0.917715220833333
00:52:52.648 --> 00:52:54.760 of experiments I didn't talk about,
NOTE Confidence: 0.917715220833333
00:52:54.760 --> 00:52:59.548 we there there was identified a an
NOTE Confidence: 0.917715220833333
00:52:59.548 --> 00:53:01.124 estrogen related molecule that's
NOTE Confidence: 0.917715220833333
00:53:01.124 --> 00:53:03.178 actually pretty effective for the
NOTE Confidence: 0.917715220833333
00:53:03.178 --> 00:53:05.238 alanine tract expansion mouse mutants.
NOTE Confidence: 0.917715220833333
00:53:05.240 --> 00:53:07.544 And Jeff Nobles and at Baylor gave this
NOTE Confidence: 0.917715220833333
00:53:07.544 --> 00:53:09.219 estrogen to these mice and actually
NOTE Confidence: 0.917715220833333
00:53:09.219 --> 00:53:11.467 did a very nice job at improving them
NOTE Confidence: 0.917715220833333
00:53:11.467 --> 00:53:13.679 and that went into a clinical trial
NOTE Confidence: 0.917715220833333
00:53:13.679 --> 00:53:16.415 which I actually don't know the results of.
NOTE Confidence: 0.917715220833333

00:53:16.420 --> 00:53:19.756 It also has led to several different groups
NOTE Confidence: 0.917715220833333

00:53:19.756 --> 00:53:23.655 now looking at replacing the inhibitory
NOTE Confidence: 0.917715220833333

00:53:23.655 --> 00:53:26.458 neurons using differentiated IPSC cells.
NOTE Confidence: 0.917715220833333

00:53:26.458 --> 00:53:28.612 And so you're specifically looking at
NOTE Confidence: 0.917715220833333

00:53:28.612 --> 00:53:30.655 not just differentiated inter neurons
NOTE Confidence: 0.917715220833333

00:53:30.655 --> 00:53:33.602 but even subtypes which I didn't really
NOTE Confidence: 0.917715220833333

00:53:33.664 --> 00:53:36.199 talk about specifically parvalbumin as
NOTE Confidence: 0.917715220833333

00:53:36.199 --> 00:53:38.734 opposed to the somatostatin subpopulations.
NOTE Confidence: 0.917715220833333

00:53:38.740 --> 00:53:40.676 I also hope that I've given you a
NOTE Confidence: 0.917715220833333

00:53:40.676 --> 00:53:42.295 little bit insight how different
NOTE Confidence: 0.917715220833333

00:53:42.295 --> 00:53:44.670 mutations in the same gene.
NOTE Confidence: 0.917715220833333

00:53:44.670 --> 00:53:47.190 Can result in two different phenotypes.
NOTE Confidence: 0.917715220833333

00:53:47.190 --> 00:53:49.350 So when you lose that gene you you affect
NOTE Confidence: 0.917715220833333

00:53:49.350 --> 00:53:51.430 both excitatory and inhibitory neurons,
NOTE Confidence: 0.917715220833333

00:53:51.430 --> 00:53:52.750 at least for a RX,
NOTE Confidence: 0.917715220833333

00:53:52.750 --> 00:53:54.230 whereas the alanine tract

NOTE Confidence: 0.917715220833333

00:53:54.230 --> 00:53:56.450 expansion only seem to affect one

NOTE Confidence: 0.917715220833333

00:53:56.518 --> 00:53:58.590 population of inhibitory neurons,

NOTE Confidence: 0.917715220833333

00:53:58.590 --> 00:54:00.250 giving you different phenotypes

NOTE Confidence: 0.917715220833333

00:54:00.250 --> 00:54:02.740 in these different cell types and

NOTE Confidence: 0.917715220833333

00:54:02.809 --> 00:54:04.789 therefore different phenotypes.

NOTE Confidence: 0.917715220833333

00:54:04.790 --> 00:54:05.402 I've also,

NOTE Confidence: 0.917715220833333

00:54:05.402 --> 00:54:06.626 through the mitochondria work,

NOTE Confidence: 0.917715220833333

00:54:06.630 --> 00:54:09.062 talked about how metabolic

NOTE Confidence: 0.917715220833333

00:54:09.062 --> 00:54:12.034 perturbations in the inhibitory neurons.

NOTE Confidence: 0.917715220833333

00:54:12.034 --> 00:54:14.398 Because they require that

NOTE Confidence: 0.917715220833333

00:54:14.398 --> 00:54:15.580 oxidated phosphorylation,

NOTE Confidence: 0.917715220833333

00:54:15.580 --> 00:54:17.358 they no longer are able to function

NOTE Confidence: 0.917715220833333

00:54:17.358 --> 00:54:19.190 and I think this contributes to

NOTE Confidence: 0.917715220833333

00:54:19.190 --> 00:54:20.870 the phenotype in these patients

NOTE Confidence: 0.917715220833333

00:54:20.870 --> 00:54:22.852 and really should we should start

NOTE Confidence: 0.917715220833333

00:54:22.852 --> 00:54:24.736 thinking about new ways for therapy
NOTE Confidence: 0.917715220833333
00:54:24.740 --> 00:54:27.890 as opposed to just trying to correct
NOTE Confidence: 0.917715220833333
00:54:27.890 --> 00:54:30.739 the energetics in the brain itself.
NOTE Confidence: 0.917715220833333
00:54:30.740 --> 00:54:34.350 So let me end there and really thank
NOTE Confidence: 0.917715220833333
00:54:34.350 --> 00:54:36.180 the people that have done this.
NOTE Confidence: 0.917715220833333
00:54:36.180 --> 00:54:38.328 All the recent work on the marijuana
NOTE Confidence: 0.917715220833333
00:54:38.328 --> 00:54:40.380 has been done by a postdoc in my lab,
NOTE Confidence: 0.917715220833333
00:54:40.380 --> 00:54:41.348 Abby Myers,
NOTE Confidence: 0.917715220833333
00:54:41.348 --> 00:54:46.076 who just now has a job as a as an
NOTE Confidence: 0.917715220833333
00:54:46.076 --> 00:54:48.216 assistant professor at Hamilton College.
NOTE Confidence: 0.917715220833333
00:54:48.220 --> 00:54:51.124 The work on the Alanine tract
NOTE Confidence: 0.917715220833333
00:54:51.124 --> 00:54:53.860 expansion was done by AM DPHD
NOTE Confidence: 0.917715220833333
00:54:53.860 --> 00:54:57.288 student in in my lab a while back.
NOTE Confidence: 0.917715220833333
00:54:57.288 --> 00:54:58.716 MacLean is Ralia.
NOTE Confidence: 0.917715220833333
00:54:58.720 --> 00:55:01.254 All the epilepsy work is done in
NOTE Confidence: 0.917715220833333
00:55:01.254 --> 00:55:02.800 collaboration with Eric Marsh,

NOTE Confidence: 0.917715220833333
00:55:02.800 --> 00:55:04.800 who was a postdoc in my lab and
NOTE Confidence: 0.917715220833333
00:55:04.800 --> 00:55:06.680 we still collaborate together.
NOTE Confidence: 0.917715220833333
00:55:06.680 --> 00:55:10.886 And the some of the other work I I
NOTE Confidence: 0.917715220833333
00:55:10.886 --> 00:55:13.439 mentioned was done by Erica Lynn Hendel.
NOTE Confidence: 0.917715220833333
00:55:13.439 --> 00:55:16.637 She did the early mitochondrial work
NOTE Confidence: 0.917715220833333
00:55:16.637 --> 00:55:20.157 and all of this is supported and and
NOTE Confidence: 0.917715220833333
00:55:20.160 --> 00:55:24.896 really my labs been largely run I would
NOTE Confidence: 0.917715220833333
00:55:24.896 --> 00:55:28.030 say by Ginam Cho and now young Shin Lin.
NOTE Confidence: 0.917715220833333
00:55:28.030 --> 00:55:29.390 As they've been with me
NOTE Confidence: 0.917715220833333
00:55:29.390 --> 00:55:30.750 for a number of years.
NOTE Confidence: 0.917715220833333
00:55:30.750 --> 00:55:32.080 So with that I'll stop and I'm
NOTE Confidence: 0.917715220833333
00:55:32.080 --> 00:55:33.309 happy to take any questions.
NOTE Confidence: 0.917715220833333
00:55:33.310 --> 00:55:34.670 Thank you very much.
NOTE Confidence: 0.9301902
00:55:40.870 --> 00:55:41.350 Yes,
NOTE Confidence: 0.943608066666667
00:55:44.750 --> 00:55:47.550 didn't show any data,
NOTE Confidence: 0.9402536

00:55:47.550 --> 00:55:48.630 but what about
NOTE Confidence: 0.9402536

00:55:51.270 --> 00:55:51.430 this
NOTE Confidence: 0.9905706

00:55:53.590 --> 00:55:55.708 polarization microphone may actually be
NOTE Confidence: 0.87457219

00:55:59.270 --> 00:56:01.070 that could affect migration?
NOTE Confidence: 0.917956666666667

00:56:02.120 --> 00:56:04.316 Yeah, yeah. So I you're right,
NOTE Confidence: 0.917956666666667

00:56:04.320 --> 00:56:07.080 I didn't show we we have done the
NOTE Confidence: 0.917956666666667

00:56:07.080 --> 00:56:08.982 the energetics data looking at a
NOTE Confidence: 0.917956666666667

00:56:08.982 --> 00:56:10.952 TP localization in the cell and
NOTE Confidence: 0.917956666666667

00:56:10.952 --> 00:56:12.557 it's it's kind of interesting.
NOTE Confidence: 0.917956666666667

00:56:12.560 --> 00:56:13.540 I'll come to your calcium
NOTE Confidence: 0.917956666666667

00:56:13.540 --> 00:56:14.520 question in just a second.
NOTE Confidence: 0.917956666666667

00:56:14.520 --> 00:56:15.896 It's actually very interesting.
NOTE Confidence: 0.917956666666667

00:56:15.896 --> 00:56:17.960 If you look at adult neurons,
NOTE Confidence: 0.917956666666667

00:56:17.960 --> 00:56:21.230 mitochondria actually have to go out
NOTE Confidence: 0.917956666666667

00:56:21.230 --> 00:56:24.435 into the into the processes of the
NOTE Confidence: 0.917956666666667

00:56:24.435 --> 00:56:26.930 cell mostly the dendrites where new.

NOTE Confidence: 0.917956666666667
00:56:26.930 --> 00:56:28.602 Synapses are being formed.
NOTE Confidence: 0.917956666666667
00:56:28.602 --> 00:56:30.692 So synaptic plasticity is highly
NOTE Confidence: 0.917956666666667
00:56:30.692 --> 00:56:32.427 dependent on mitochondria being
NOTE Confidence: 0.917956666666667
00:56:32.427 --> 00:56:34.517 shuttled through this same mechanism
NOTE Confidence: 0.917956666666667
00:56:34.517 --> 00:56:36.725 along with molecular motors out to
NOTE Confidence: 0.917956666666667
00:56:36.725 --> 00:56:39.038 those sites and then they move back
NOTE Confidence: 0.917956666666667
00:56:39.038 --> 00:56:41.126 as those synapses are being formed.
NOTE Confidence: 0.917956666666667
00:56:41.130 --> 00:56:41.490 We think
NOTE Confidence: 0.9402536
00:56:47.150 --> 00:56:48.560 that's a similar defect the cell
NOTE Confidence: 0.9402536
00:56:48.560 --> 00:56:50.150 and in your it isn't heard.
NOTE Confidence: 0.9402536
00:56:50.150 --> 00:56:51.930 I haven't I am showing we have done a little
NOTE Confidence: 0.9402536
00:56:51.972 --> 00:56:53.505 bit of calcium signaling on with this.
NOTE Confidence: 0.9402536
00:56:53.510 --> 00:56:55.382 We've done it more to look at the epilepsy
NOTE Confidence: 0.9402536
00:56:55.382 --> 00:56:57.511 and looking at the calcium waves for example
NOTE Confidence: 0.9402536
00:56:57.511 --> 00:56:59.180 in the hippocampus and in the cortex.
NOTE Confidence: 0.9402536

00:56:59.180 --> 00:57:01.820 And and there are significant abnormalities.

NOTE Confidence: 0.9402536

00:57:01.820 --> 00:57:04.230 We have not yet looked at it in terms of

NOTE Confidence: 0.9402536

00:57:04.290 --> 00:57:06.578 intracellular localization of calcium,

NOTE Confidence: 0.9402536

00:57:06.580 --> 00:57:08.460 which as you know is is a little bit harder.

NOTE Confidence: 0.9402536

00:57:08.460 --> 00:57:11.660 But we that that is something I'd like to do,

NOTE Confidence: 0.9402536

00:57:11.660 --> 00:57:12.738 but we just haven't done that yet.

NOTE Confidence: 0.9402536

00:57:12.740 --> 00:57:15.700 Yeah. Yeah. So wondering if you

NOTE Confidence: 0.9603804

00:57:17.980 --> 00:57:24.164 follow that, but the certain fact is that

NOTE Confidence: 0.9603804

00:57:24.164 --> 00:57:26.724 underlying the sociability and anxiety.

NOTE Confidence: 0.9603804

00:57:26.730 --> 00:57:29.530 The same circuits affected by epilepsy or

NOTE Confidence: 0.9402536

00:57:33.210 --> 00:57:36.820 yeah, it's it's hard to disentangle

NOTE Confidence: 0.9402536

00:57:36.820 --> 00:57:39.222 that we think So at least the one

NOTE Confidence: 0.9402536

00:57:39.222 --> 00:57:41.088 circuit we have we think correlates

NOTE Confidence: 0.9402536

00:57:41.088 --> 00:57:43.325 very nicely with some of the one of

NOTE Confidence: 0.9402536

00:57:43.325 --> 00:57:44.850 the behavioral phenotypes that we have.

NOTE Confidence: 0.9352219

00:57:46.930 --> 00:57:49.654 When you look at these mice

NOTE Confidence: 0.9352219

00:57:49.654 --> 00:57:52.150 and the epilepsy we see a.

NOTE Confidence: 0.9352219

00:57:52.150 --> 00:57:54.448 Simultaneous disorganization of

NOTE Confidence: 0.9352219

00:57:54.448 --> 00:57:57.670 electrical activity in in both

NOTE Confidence: 0.9352219

00:57:57.670 --> 00:57:59.510 hemispheres and both hippocampus.

NOTE Confidence: 0.9352219

00:57:59.510 --> 00:58:03.011 So when we when we do our analysis,

NOTE Confidence: 0.9352219

00:58:03.011 --> 00:58:05.537 we put two frontal electrodes in

NOTE Confidence: 0.9352219

00:58:05.537 --> 00:58:07.829 and two hippocampus electrodes in.

NOTE Confidence: 0.9352219

00:58:07.830 --> 00:58:10.270 So we're recording 4 sites

NOTE Confidence: 0.9352219

00:58:10.270 --> 00:58:12.600 simultaneously in these mice and

NOTE Confidence: 0.9352219

00:58:12.600 --> 00:58:14.450 we see disorganization of the

NOTE Confidence: 0.9352219

00:58:14.450 --> 00:58:16.442 cortex in and the hippocampus

NOTE Confidence: 0.9352219

00:58:16.442 --> 00:58:19.052 in all areas and seizures can

NOTE Confidence: 0.9352219

00:58:19.052 --> 00:58:20.788 come from different locations.

NOTE Confidence: 0.9352219

00:58:20.790 --> 00:58:22.785 So we don't think it's circuit specific.

NOTE Confidence: 0.9352219

00:58:22.790 --> 00:58:25.400 We think it's a more generalized

NOTE Confidence: 0.9352219

00:58:25.400 --> 00:58:27.790 disorganization of the of all the circuits.

NOTE Confidence: 0.9402536

00:58:30.190 --> 00:58:30.510 Yeah,

NOTE Confidence: 0.9654121

00:58:35.710 --> 00:58:36.630 yeah, absolutely.

NOTE Confidence: 0.9402536

00:58:46.350 --> 00:58:46.710 Yeah.

NOTE Confidence: 0.6223776

00:58:54.210 --> 00:58:58.651 Yeah, yeah. So we, we started to look

NOTE Confidence: 0.6223776

00:58:58.651 --> 00:59:01.430 at both fission and fusion and and

NOTE Confidence: 0.6223776

00:59:01.430 --> 00:59:03.685 unfortunately those experiments had fizzled.

NOTE Confidence: 0.6223776

00:59:03.690 --> 00:59:06.430 So I don't have any data to

NOTE Confidence: 0.6223776

00:59:06.430 --> 00:59:08.690 show you we tried to do that.

NOTE Confidence: 0.6223776

00:59:08.690 --> 00:59:11.386 We do think that it's a failure of

NOTE Confidence: 0.6223776

00:59:11.386 --> 00:59:12.810 fission as opposed to a fusion.

NOTE Confidence: 0.6223776

00:59:12.810 --> 00:59:15.960 We think they can break apart, but.

NOTE Confidence: 0.6223776

00:59:15.960 --> 00:59:18.610 When we've studied that, we've studied

NOTE Confidence: 0.6223776

00:59:18.610 --> 00:59:21.400 that in a couple different ways.

NOTE Confidence: 0.6223776

00:59:21.400 --> 00:59:23.696 The cells get really sick when we

NOTE Confidence: 0.6223776

00:59:23.696 --> 00:59:25.959 try and disrupt that specifically.

NOTE Confidence: 0.6223776

00:59:25.960 --> 00:59:27.640 And so I don't think we,

NOTE Confidence: 0.6223776

00:59:27.640 --> 00:59:29.158 the cells get sick, they die,

NOTE Confidence: 0.6223776

00:59:29.160 --> 00:59:30.516 they don't move, they don't divide,

NOTE Confidence: 0.6223776

00:59:30.520 --> 00:59:32.200 they don't do a lot of things.

NOTE Confidence: 0.6223776

00:59:32.200 --> 00:59:33.256 And so that's been a really

NOTE Confidence: 0.6223776

00:59:33.256 --> 00:59:34.359 hard thing for us to study,

NOTE Confidence: 0.6223776

00:59:34.360 --> 00:59:35.520 at least in these neurons.

NOTE Confidence: 0.6223776

00:59:35.520 --> 00:59:38.240 I know you can study it in other cell types,

NOTE Confidence: 0.6223776

00:59:38.240 --> 00:59:40.207 but when we try and introduce some

NOTE Confidence: 0.6223776

00:59:40.207 --> 00:59:42.070 of those genes that are involved

NOTE Confidence: 0.6223776

00:59:42.070 --> 00:59:43.996 in both fission and fusion or

NOTE Confidence: 0.6223776

00:59:43.996 --> 00:59:46.156 actually we've disrupted them. It is.

NOTE Confidence: 0.6223776

00:59:46.156 --> 00:59:48.460 It is not gone very well for us.

NOTE Confidence: 0.6223776

00:59:48.460 --> 00:59:49.979 So I wish I could answer that.

NOTE Confidence: 0.6223776

00:59:49.980 --> 00:59:50.720 We've tried.

NOTE Confidence: 0.6223776

00:59:50.720 --> 00:59:52.940 It's a it's a great question

NOTE Confidence: 0.6223776

00:59:52.940 --> 00:59:54.256 and I'd like to get an answer,

NOTE Confidence: 0.6223776

00:59:54.260 --> 00:59:57.540 but that's been a hard thing to study.

NOTE Confidence: 0.6223776

00:59:57.540 --> 00:59:57.900 Yes Sir,

NOTE Confidence: 0.850692246

01:00:00.940 --> 01:00:02.764 totally something that

NOTE Confidence: 0.850692246

01:00:02.764 --> 01:00:05.084 I'm told it got wrong.

NOTE Confidence: 0.850692246

01:00:05.084 --> 01:00:07.806 So I'm really fascinated to try to

NOTE Confidence: 0.850692246

01:00:07.806 --> 01:00:10.152 connect with 1/3 of the dollars.

NOTE Confidence: 0.850692246

01:00:10.152 --> 01:00:12.240 Seems like there is a rather

NOTE Confidence: 0.850692246

01:00:12.240 --> 01:00:13.920 large gap in there.

NOTE Confidence: 0.850692246

01:00:13.920 --> 01:00:17.838 I don't get any together or

NOTE Confidence: 0.850692246

01:00:17.840 --> 01:00:20.070 just one basic question is

NOTE Confidence: 0.850692246

01:00:20.070 --> 01:00:23.520 that's the thing just seems

NOTE Confidence: 0.9603802925

01:00:25.920 --> 01:00:27.680 like there's this behavioral.

NOTE Confidence: 0.946657475454545

01:00:34.680 --> 01:00:36.612 Yeah, you're right. It's a big

NOTE Confidence: 0.946657475454545

01:00:36.612 --> 01:00:38.640 jump from molecular to behavioral.

NOTE Confidence: 0.946657475454545

01:00:38.640 --> 01:00:40.464 But that is what we're trying to piece

NOTE Confidence: 0.946657475454545

01:00:40.464 --> 01:00:42.160 together one, one part at a time.

NOTE Confidence: 0.942266388

01:00:44.490 --> 01:00:48.472 In terms of the specificity, the behavior

NOTE Confidence: 0.942266388

01:00:48.472 --> 01:00:52.327 is actually becomes very specific.

NOTE Confidence: 0.942266388

01:00:52.330 --> 01:00:54.298 Why can I say that? Well, we do,

NOTE Confidence: 0.942266388

01:00:54.298 --> 01:00:56.370 you do this whole battery of tests,

NOTE Confidence: 0.942266388

01:00:56.370 --> 01:00:57.418 we did smell tests.

NOTE Confidence: 0.942266388

01:00:57.418 --> 01:00:58.990 You do these bearing of different

NOTE Confidence: 0.942266388

01:00:59.039 --> 01:01:00.491 marbles and things like that and

NOTE Confidence: 0.942266388

01:01:00.491 --> 01:01:02.447 look at how fast they can find them.

NOTE Confidence: 0.942266388

01:01:02.450 --> 01:01:07.985 You can do these memory tests you can do.

NOTE Confidence: 0.942266388

01:01:07.990 --> 01:01:09.430 You you have to test gate,

NOTE Confidence: 0.942266388

01:01:09.430 --> 01:01:11.190 you have to test strength because if they,

NOTE Confidence: 0.942266388

01:01:11.190 --> 01:01:12.210 if they're not strong enough

NOTE Confidence: 0.942266388

01:01:12.210 --> 01:01:13.358 or they can't walk, they don't,

NOTE Confidence: 0.942266388

01:01:13.358 --> 01:01:14.506 they can't do some of these things,
NOTE Confidence: 0.942266388

01:01:14.510 --> 01:01:17.390 they won't go over and see that other mouse.
NOTE Confidence: 0.942266388

01:01:17.390 --> 01:01:20.134 So there's a whole battery of tests we
NOTE Confidence: 0.942266388

01:01:20.134 --> 01:01:22.592 do and show that they're all normal.
NOTE Confidence: 0.942266388

01:01:22.592 --> 01:01:24.596 I mean these mice behave normally
NOTE Confidence: 0.942266388

01:01:24.596 --> 01:01:26.546 in in almost all these tests,
NOTE Confidence: 0.942266388

01:01:26.550 --> 01:01:29.028 but it gets very specific for these
NOTE Confidence: 0.942266388

01:01:29.028 --> 01:01:30.459 socialization tests where we've
NOTE Confidence: 0.942266388

01:01:30.459 --> 01:01:33.197 see all the defects. So the the,
NOTE Confidence: 0.942266388

01:01:33.197 --> 01:01:36.760 the specificity of it is very good.
NOTE Confidence: 0.942266388

01:01:36.760 --> 01:01:37.760 Now the next step, though,
NOTE Confidence: 0.942266388

01:01:37.760 --> 01:01:40.176 is what does it mean? I mean,
NOTE Confidence: 0.942266388

01:01:40.176 --> 01:01:41.606 that's the anthropomorphosizing, right?
NOTE Confidence: 0.942266388

01:01:41.606 --> 01:01:43.836 What is an autistic mouse?
NOTE Confidence: 0.942266388

01:01:43.840 --> 01:01:45.880 I mean, you don't really know that, right?
NOTE Confidence: 0.942266388

01:01:45.880 --> 01:01:49.520 So we use these kind of surrogates

NOTE Confidence: 0.942266388

01:01:49.520 --> 01:01:52.640 that the field has, has adopted to use.

NOTE Confidence: 0.942266388

01:01:52.640 --> 01:01:55.680 And and that's, I think, the best we can do.

NOTE Confidence: 0.942266388

01:01:55.680 --> 01:01:56.680 But there is, I think,

NOTE Confidence: 0.942266388

01:01:56.680 --> 01:01:58.040 a high degree of specificity.

NOTE Confidence: 0.946962478333333

01:02:01.160 --> 01:02:02.219 2 questions. First,

NOTE Confidence: 0.946962478333333

01:02:02.219 --> 01:02:04.888 have you gone beyond the fact you

NOTE Confidence: 0.946962478333333

01:02:04.888 --> 01:02:06.496 have a transcriptional regulator?

NOTE Confidence: 0.946962478333333

01:02:06.500 --> 01:02:10.902 And there's migratory in terms of

NOTE Confidence: 0.946962478333333

01:02:10.902 --> 01:02:12.346 looking the downstream mechanism

NOTE Confidence: 0.946962478333333

01:02:12.346 --> 01:02:14.420 and what are the gradients

NOTE Confidence: 0.946962478333333

01:02:14.420 --> 01:02:17.044 there caused in migratory.

NOTE Confidence: 0.946962478333333

01:02:17.044 --> 01:02:19.218 And I'll give you the second question,

NOTE Confidence: 0.946962478333333

01:02:19.220 --> 01:02:22.180 if you look at stamping structure,

NOTE Confidence: 0.946962478333333

01:02:22.180 --> 01:02:25.180 please sample any change there.

NOTE Confidence: 0.930190133333333

01:02:30.540 --> 01:02:32.370 I don't have it in here. Yeah.

NOTE Confidence: 0.930190133333333

01:02:32.370 --> 01:02:35.050 So we actually published.
NOTE Confidence: 0.9301901333333333

01:02:35.050 --> 01:02:35.876 Several articles.
NOTE Confidence: 0.9301901333333333

01:02:35.876 --> 01:02:37.808 They're all in J. Neuroscience.
NOTE Confidence: 0.9301901333333333

01:02:37.808 --> 01:02:39.754 Dan Lysco was a graduate student in
NOTE Confidence: 0.9301901333333333

01:02:39.754 --> 01:02:41.732 my lab who was really interested in
NOTE Confidence: 0.9301901333333333

01:02:41.732 --> 01:02:44.086 this and and he started looking at
NOTE Confidence: 0.9301901333333333

01:02:44.086 --> 01:02:45.470 gradients of different molecules
NOTE Confidence: 0.9301901333333333

01:02:45.534 --> 01:02:47.580 and their role in the migration
NOTE Confidence: 0.9301901333333333

01:02:47.580 --> 01:02:49.876 and actually connecting the
NOTE Confidence: 0.9301901333333333

01:02:49.876 --> 01:02:53.190 gradients of different things,
NOTE Confidence: 0.9301901333333333

01:02:53.190 --> 01:02:55.140 particularly in the wind signaling
NOTE Confidence: 0.9301901333333333

01:02:55.140 --> 01:02:57.090 pathway which is expressed
NOTE Confidence: 0.9301901333333333

01:02:57.090 --> 01:03:00.978 both in the meninges and in the
NOTE Confidence: 0.9301901333333333

01:03:00.978 --> 01:03:03.306 that that migratory stream.
NOTE Confidence: 0.9301901333333333

01:03:03.310 --> 01:03:06.154 And show that that went signaling
NOTE Confidence: 0.9301901333333333

01:03:06.154 --> 01:03:08.625 going through the receptors through

NOTE Confidence: 0.9301901333333333

01:03:08.625 --> 01:03:10.613 the frizzled receptors actually

NOTE Confidence: 0.9301901333333333

01:03:10.613 --> 01:03:14.111 connects to the micro to the both

NOTE Confidence: 0.9301901333333333

01:03:14.111 --> 01:03:15.922 actin and microtubule cytoskeleton

NOTE Confidence: 0.9301901333333333

01:03:15.922 --> 01:03:18.806 and affects the ability of that to

NOTE Confidence: 0.9301901333333333

01:03:18.806 --> 01:03:21.070 branch and do things in the migration.

NOTE Confidence: 0.921062423

01:03:27.990 --> 01:03:31.448 So, so that and. And also the

NOTE Confidence: 0.921062423

01:03:31.448 --> 01:03:34.698 the other one actually that he

NOTE Confidence: 0.921062423

01:03:34.698 --> 01:03:38.920 studied even more was SD F4 and so

NOTE Confidence: 0.9346628222222222

01:03:42.160 --> 01:03:45.104 CDCX CR4 and CX CL12 which is the

NOTE Confidence: 0.9346628222222222

01:03:45.104 --> 01:03:47.436 ligand and he was able to show

NOTE Confidence: 0.9346628222222222

01:03:47.436 --> 01:03:49.358 that those are modulated by a RX.

NOTE Confidence: 0.943128857142857

01:03:52.000 --> 01:03:53.519 We haven't looked at all at synaptic,

NOTE Confidence: 0.943128857142857

01:03:53.520 --> 01:03:54.955 it would be another area to go,

NOTE Confidence: 0.943128857142857

01:03:54.960 --> 01:03:57.320 but we have not done that, yeah.

NOTE Confidence: 0.93019015

01:04:01.560 --> 01:04:05.000 Look at the difference that make this

NOTE Confidence: 0.9503169

01:04:07.040 --> 01:04:11.080 thing to run out or in
NOTE Confidence: 0.933544596666667

01:04:14.000 --> 01:04:14.879 human and so
NOTE Confidence: 0.948304255

01:04:17.840 --> 01:04:21.008 we've kind of we've done descriptive
NOTE Confidence: 0.948304255

01:04:21.008 --> 01:04:24.572 pathology in the human and we've been able
NOTE Confidence: 0.948304255

01:04:24.572 --> 01:04:28.068 to look at 2 humans with a RX mutations.
NOTE Confidence: 0.948304255

01:04:28.070 --> 01:04:29.918 And they do have a deficit in
NOTE Confidence: 0.948304255

01:04:29.918 --> 01:04:31.126 the inhibitory neurons that's
NOTE Confidence: 0.948304255

01:04:31.126 --> 01:04:32.906 greater than their excitatory ones.
NOTE Confidence: 0.948304255

01:04:32.910 --> 01:04:34.950 But the the two brains we've looked at
NOTE Confidence: 0.948304255

01:04:34.950 --> 01:04:36.988 both had the Liz encephalophenotype.
NOTE Confidence: 0.948304255

01:04:36.990 --> 01:04:39.160 So they also had a, a structural defect.
NOTE Confidence: 0.948304255

01:04:39.160 --> 01:04:42.310 So it wasn't so easy to parse that out.
NOTE Confidence: 0.948304255

01:04:42.310 --> 01:04:43.590 And then we, you know,
NOTE Confidence: 0.948304255

01:04:43.590 --> 01:04:45.110 most of the works been in the mouse.
NOTE Confidence: 0.948304255

01:04:45.110 --> 01:04:46.268 We have not been able to,
NOTE Confidence: 0.948304255

01:04:46.270 --> 01:04:48.722 we've not done anything in the humans in

NOTE Confidence: 0.948304255

01:04:48.722 --> 01:04:50.864 terms of trying to study the migration,

NOTE Confidence: 0.948304255

01:04:50.870 --> 01:04:52.910 but we'd like to do that.

NOTE Confidence: 0.948304255

01:04:52.910 --> 01:04:57.102 And just recently, I've gotten 2 patients.

NOTE Confidence: 0.948304255

01:04:57.102 --> 01:04:59.326 They're they're actually brothers

NOTE Confidence: 0.948304255

01:04:59.326 --> 01:05:02.580 that have a RX mutations.

NOTE Confidence: 0.948304255

01:05:02.580 --> 01:05:04.458 The parents have consented and we've

NOTE Confidence: 0.948304255

01:05:04.458 --> 01:05:06.938 gotten and we're in the process of making

NOTE Confidence: 0.948304255

01:05:06.940 --> 01:05:09.580 iPSC's from those ARX mutation patients,

NOTE Confidence: 0.948304255

01:05:09.580 --> 01:05:12.140 which are going to allow us to then

NOTE Confidence: 0.948304255

01:05:12.140 --> 01:05:15.019 look at the migration of those cells,

NOTE Confidence: 0.948304255

01:05:15.020 --> 01:05:16.798 both putting them into like nude mice

NOTE Confidence: 0.948304255

01:05:16.798 --> 01:05:19.040 but also in culture to be able to study

NOTE Confidence: 0.948304255

01:05:19.040 --> 01:05:21.075 how do they behave when we differentiate

NOTE Confidence: 0.948304255

01:05:21.075 --> 01:05:23.469 them to inner neurons or excitatory neurons.

NOTE Confidence: 0.948304255

01:05:23.470 --> 01:05:25.504 So that is the next step to kind of

NOTE Confidence: 0.948304255

01:05:25.504 --> 01:05:27.323 make that transition and understand

NOTE Confidence: 0.948304255

01:05:27.323 --> 01:05:29.627 what's the relationship of these two,

NOTE Confidence: 0.948304255

01:05:29.630 --> 01:05:30.264 the humans.

NOTE Confidence: 0.948304255

01:05:30.264 --> 01:05:32.483 So that's what we're doing right now

NOTE Confidence: 0.948304255

01:05:32.483 --> 01:05:34.590 to do that and I'm excited to have

NOTE Confidence: 0.948304255

01:05:34.590 --> 01:05:36.150 these two patients and grateful there

NOTE Confidence: 0.90374499

01:05:41.150 --> 01:05:44.732 is some evidence. Yeah.

NOTE Confidence: 0.90374499

01:05:44.732 --> 01:05:46.420 So I think that's.

NOTE Confidence: 0.90374499

01:05:46.420 --> 01:05:48.332 So to work that you did a number

NOTE Confidence: 0.90374499

01:05:48.332 --> 01:05:50.367 of years ago that was published in

NOTE Confidence: 0.90374499

01:05:50.367 --> 01:05:52.291 Neuron and then work that Thomas

NOTE Confidence: 0.90374499

01:05:52.291 --> 01:05:54.446 Noakowski at UCSF has recently

NOTE Confidence: 0.90374499

01:05:54.446 --> 01:05:57.069 done doing single cell work really

NOTE Confidence: 0.90374499

01:05:57.069 --> 01:05:59.939 I think defines that there is a

NOTE Confidence: 0.90374499

01:05:59.939 --> 01:06:01.619 subpopulation of the inhibitory

NOTE Confidence: 0.90374499

01:06:01.619 --> 01:06:03.614 neurons that are coming from

NOTE Confidence: 0.90374499
01:06:03.614 --> 01:06:05.460 the cortical ventricular zone.
NOTE Confidence: 0.942998163636364
01:06:07.980 --> 01:06:09.744 All the studies in mice don't
NOTE Confidence: 0.942998163636364
01:06:09.744 --> 01:06:11.260 seem to have supported that.
NOTE Confidence: 0.942998163636364
01:06:11.260 --> 01:06:12.860 That's at least my feeling from it you.
NOTE Confidence: 0.942998163636364
01:06:12.860 --> 01:06:13.820 Yeah, but I I didn't see yet.
NOTE Confidence: 0.6285699
01:06:16.920 --> 01:06:20.760 Maybe, yes Marks. Yeah. Yeah.
NOTE Confidence: 0.938576485
01:06:28.600 --> 01:06:29.878 Yeah. So I think that's right.
NOTE Confidence: 0.938576485
01:06:29.880 --> 01:06:31.665 And I do think that there are
NOTE Confidence: 0.938576485
01:06:31.665 --> 01:06:33.045 those cells that are coming
NOTE Confidence: 0.938576485
01:06:33.045 --> 01:06:35.104 from there and by studying these
NOTE Confidence: 0.938576485
01:06:35.104 --> 01:06:36.328 ipsc's and differentiating
NOTE Confidence: 0.938576485
01:06:36.328 --> 01:06:37.960 them along different lines,
NOTE Confidence: 0.938576485
01:06:37.960 --> 01:06:40.120 we should be able to get at these answers.
NOTE Confidence: 0.938576485
01:06:40.120 --> 01:06:41.040 But I don't know now
NOTE Confidence: 0.957026046666667
01:06:44.040 --> 01:06:46.720 any other questions? All right.
NOTE Confidence: 0.957026046666667

01:06:46.720 --> 01:06:47.995 Well, thank you very much.