WEBVTT

NOTE duration:"01:06:48"

NOTE recognizability:0.923

NOTE language:en-us

NOTE Confidence: 0.8572010466666667

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

NOTE Confidence: 0.95786455

 $00:00:01.960 \longrightarrow 00:00:05.680$ everyone. Thanks for coming today.

NOTE Confidence: 0.95786455

 $00:00:05.680 \rightarrow 00:00:10.090$ It is my honor to introduce my friend

NOTE Confidence: 0.95786455

 $00:00:10.090 \rightarrow 00:00:13.420$ and mentor and fellow neuropathologist,

NOTE Confidence: 0.95786455

 $00:00:13.420 \longrightarrow 00:00:15.520$ 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

 $00:00:17.718 \longrightarrow 00:00:20.237$ 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

 $00{:}00{:}24.160 \dashrightarrow 00{:}00{:}26.080$ the Burns and Allen Research.

NOTE Confidence: 0.95786455

 $00{:}00{:}26.080 \dashrightarrow 00{:}00{:}28.816$ Institute at Cedars Sinai and also the Vice

NOTE Confidence: 0.95786455

 $00{:}00{:}28.816 \dashrightarrow 00{:}00{:}31.719$ Dean of Research and Graduate Education.

NOTE Confidence: 0.95786455

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

00:00:33.730 --> 00:00:35.740 of Pennsylvania School of Medicine NOTE Confidence: 0.95786455 $00{:}00{:}35{.}800 \dashrightarrow 00{:}00{:}38{.}236$ and after that went on to do NOTE Confidence: 0.95786455 $00:00:38.236 \rightarrow 00:00:39.280$ 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 $00:00:42.717 \dashrightarrow 00:00:45.216$ 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 $00:00:47.324 \longrightarrow 00:00:49.652$ his career into studying the NOTE Confidence: 0.95786455 $00:00:49.652 \rightarrow 00:00:52.072$ 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 $00:00:56.788 \rightarrow 00:00:59.463$ radial cell migration and its critical NOTE Confidence: 0.95786455 $00:00:59.463 \rightarrow 00:01:02.090$ role in interneuron migration during NOTE Confidence: 0.95786455 $00:01:02.090 \rightarrow 00:01:04.790$ neocortical development and his NOTE Confidence: 0.95786455 $00:01:04.790 \rightarrow 00:01:07.644$ 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
- $00{:}01{:}09{.}148 \dashrightarrow 00{:}01{:}11{.}466$ the molecular and cellular basis of

 $00{:}01{:}11{.}466 \dashrightarrow 00{:}01{:}13{.}890$ several malformations of cortical

NOTE Confidence: 0.95786455

 $00{:}01{:}13.890 \dashrightarrow 00{:}01{:}16.410$ development as well as epilepsy and

NOTE Confidence: 0.95786455

 $00:01:16.410 \dashrightarrow 00:01:21.630$ and other intellectual disorders. So I.

NOTE Confidence: 0.95786455

 $00:01:21.630 \dashrightarrow 00:01:23.390$ 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

 $00:01:26.070 \longrightarrow 00:01:27.988$ such an honor to have Jeff here.

NOTE Confidence: 0.935940714285714

 $00:01:27.990 \rightarrow 00:01:29.310$ We've been trying to get him here

NOTE Confidence: 0.935940714285714

 $00{:}01{:}29{.}310 \dashrightarrow 00{:}01{:}31{.}710$ 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: 0.932054222222222

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

NOTE Confidence: 0.932054222222222

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

NOTE Confidence: 0.93205422222222

 $00{:}01{:}43.670 \dashrightarrow 00{:}01{:}46.158$ This is I think the third of several

NOTE Confidence: 0.93205422222222

 $00{:}01{:}46.158 \dashrightarrow 00{:}01{:}47.550$ aborted attempts to get here.

 $00:01:47.550 \longrightarrow 00:01:49.694$ And so I'm really pleased to be here.

NOTE Confidence: 0.93205422222222

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

NOTE Confidence: 0.93205422222222

 $00:01:51.660 \rightarrow 00:01:53.220$ this is I think the only,

NOTE Confidence: 0.93205422222222

 $00:01:53.220 \rightarrow 00:01:55.497$ this is only my second visit to a university,

 $00:01:55.500 \longrightarrow 00:01:58.034$ so it's great to see people in

NOTE Confidence: 0.93205422222222

 $00{:}01{:}58.034 \dashrightarrow 00{:}02{:}00.490$ person and be able to start feeling

NOTE Confidence: 0.93205422222222

 $00:02:00.490 \longrightarrow 00:02:02.620$ like we're getting back to normal.

NOTE Confidence: 0.93205422222222

 $00:02:02.620 \longrightarrow 00:02:04.660$ So today what I want to

NOTE Confidence: 0.93205422222222

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

NOTE Confidence: 0.9452853

 $00:02:09.780 \longrightarrow 00:02:11.220$ we've been doing over.

NOTE Confidence: 0.95635504

 $00:02:28.560 \dashrightarrow 00:02:30.040$ Technology have started to really

NOTE Confidence: 0.9352219

 $00:02:32.160 \longrightarrow 00:02:32.840$ just out

NOTE Confidence: 0.80314445

 $00{:}02{:}35{.}040 \dashrightarrow 00{:}02{:}35{.}120$ there

NOTE Confidence: 0.926416425

 $00:02:38.340 \longrightarrow 00:02:41.035$ we go. So I like to start

NOTE Confidence: 0.926416425

 $00{:}02{:}41.035 \dashrightarrow 00{:}02{:}42.059$ out there was playing

NOTE Confidence: 0.94226628

 $00:02:44.980 \longrightarrow 00:02:46.420$ that's good okay there we

 $00:02:48.700 \rightarrow 00:02:51.780$ go case and and what you see here is a mom

NOTE Confidence: 0.934503085714286

 $00:02:54.820 \longrightarrow 00:02:58.026$ playing with her son in a crib.

NOTE Confidence: 0.934503085714286

 $00:02:58.030 \longrightarrow 00:03:00.271$ The sun has a cap on which is an

NOTE Confidence: 0.934503085714286

 $00:03:00.271 \rightarrow 00:03:02.427 \text{ EEG recording is a video EEG and}$

NOTE Confidence: 0.934503085714286

 $00:03:02.427 \longrightarrow 00:03:04.781$ and you see him almost kind of

NOTE Confidence: 0.934503085714286

 $00:03:04.781 \dashrightarrow 00:03:06.905$ flop over as if almost playing.

NOTE Confidence: 0.934503085714286

 $00{:}03{:}06{.}910 \dashrightarrow 00{:}03{:}10{.}385$ But in fact this is a what's called

NOTE Confidence: 0.934503085714286

 $00:03:10.385 \longrightarrow 00:03:12.950$ a drop seizure or a epileptic

NOTE Confidence: 0.934503085714286

 $00:03:12.950 \longrightarrow 00:03:16.150$ seizure that this child has.

NOTE Confidence: 0.934503085714286

 $00{:}03{:}16{.}150 \dashrightarrow 00{:}03{:}19{.}518$ And the type of seizure actually pretends

NOTE Confidence: 0.934503085714286

 $00:03:19.518 \rightarrow 00:03:23.186$ a very poor prognosis for this individual.

NOTE Confidence: 0.934503085714286

 $00{:}03{:}23{.}190 \dashrightarrow 00{:}03{:}26{.}414$ 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

 $00:03:29.900 \rightarrow 00:03:33.036$ seizures and became increasingly severe.

NOTE Confidence: 0.934503085714286

 $00:03:33.036 \longrightarrow 00:03:35.058$ Also had cognitive

- $00:03:37.140 \longrightarrow 00:03:39.540$ disabilities and had
- NOTE Confidence: 0.962057633333333
- $00:03:39.540 \longrightarrow 00:03:41.940$ autism spectrum disorder.
- NOTE Confidence: 0.962057633333333
- $00:03:41.940 \longrightarrow 00:03:43.780$ And so from this very simple thing we
- NOTE Confidence: 0.905285902105263
- $00:03:51.540 \rightarrow 00:03:53.908$ neurobiology that must underlie.
- NOTE Confidence: 0.905285902105263
- $00{:}03{:}53{.}908 \dashrightarrow 00{:}03{:}57{.}460$ These defects and and that's really
- NOTE Confidence: 0.905285902105263
- $00:03:57.548 \rightarrow 00:04:00.098$ what I've been thinking about for
- NOTE Confidence: 0.905285902105263
- $00:04:00.098 \dashrightarrow 00:04:01.884$ most of my scientific career.
- NOTE Confidence: 0.905285902105263
- $00:04:01.884 \rightarrow 00:04:03.900$ So let me just tell you a couple
- NOTE Confidence: 0.905285902105263
- $00:04:03.954 \rightarrow 00:04:05.616$ basic things about epilepsy and then
- NOTE Confidence: 0.905285902105263
- $00:04:05.616 \rightarrow 00:04:07.420$ we'll get into some other things.
- NOTE Confidence: 0.905285902105263
- $00:04:07.420 \rightarrow 00:04:09.304$ It's actually pretty common.
- NOTE Confidence: 0.905285902105263
- $00:04:09.304 \rightarrow 00:04:11.659$ It's more common than stroke,
- NOTE Confidence: 0.905285902105263
- $00:04:11.660 \longrightarrow 00:04:13.820$ which we hear about a lot.
- NOTE Confidence: 0.905285902105263
- $00:04:13.820 \rightarrow 00:04:17.660$ It is actually about as prevalent as asthma,
- NOTE Confidence: 0.905285902105263
- $00:04:17.660 \longrightarrow 00:04:19.658$ which is heard about a lot.
- NOTE Confidence: 0.905285902105263
- $00:04:19.660 \rightarrow 00:04:24.704$ So epilepsy is a major healthcare issue.

- NOTE Confidence: 0.905285902105263
- $00:04:24.704 \longrightarrow 00:04:29.036$ And it's really hard to control.
- NOTE Confidence: 0.58313337
- $00{:}04{:}32{.}240 \dashrightarrow 00{:}04{:}38{.}500$ Most Asian even with extensive
- NOTE Confidence: 0.58313337
- $00:04:38.500 \dashrightarrow 00:04:41.744$ multi drug therapy do not come under
- NOTE Confidence: 0.58313337
- $00:04:41.744 \rightarrow 00:04:44.558$ control and only a subset of them
- NOTE Confidence: 0.58313337
- $00{:}04{:}44{.}558 \dashrightarrow 00{:}04{:}47{.}351$ are able to be managed with surgery.
- NOTE Confidence: 0.58313337
- $00{:}04{:}47.360 \dashrightarrow 00{:}04{:}48.392$ So there are some that can
- NOTE Confidence: 0.58313337
- $00:04:48.392 \longrightarrow 00:04:49.080$ be managed with surgery,
- NOTE Confidence: 0.58313337
- $00{:}04{:}49{.}080 \dashrightarrow 00{:}04{:}51{.}110$ but it's just a subset.
- NOTE Confidence: 0.58313337
- $00{:}04{:}51{.}110 \dashrightarrow 00{:}04{:}54{.}030$ 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
- $00:04:56.430 \longrightarrow 00:04:58.510$ the underlying biology to
- NOTE Confidence: 0.58313337
- $00{:}04{:}58{.}510 \dashrightarrow 00{:}05{:}01{.}110$ really begin to think about
- NOTE Confidence: 0.58313337
- $00:05:01.110 \rightarrow 00:05:01.917$ biologically relevant therapeutics.
- NOTE Confidence: 0.58313337
- $00{:}05{:}01{.}917 \dashrightarrow 00{:}05{:}03{.}531$ So we can talk about that
- NOTE Confidence: 0.58313337
- $00{:}05{:}03{.}531 \dashrightarrow 00{:}05{:}04{.}789$ a little bit at the end.
- NOTE Confidence: 0.914410145454545

 $00:05:06.830 \rightarrow 00:05:09.049$ So what are the causes of epilepsy

NOTE Confidence: 0.914410145454545

 $00:05:09.049 \rightarrow 00:05:10.470$ where they're quite varied,

NOTE Confidence: 0.914410145454545

 $00:05:10.470 \longrightarrow 00:05:12.426$ They include things like brain injury,

NOTE Confidence: 0.914410145454545

 $00:05:12.430 \longrightarrow 00:05:15.174$ so trauma to the brain and lead

NOTE Confidence: 0.914410145454545

 $00{:}05{:}15{.}174 \dashrightarrow 00{:}05{:}18{.}298$ to its stroke tumors and there's a

NOTE Confidence: 0.914410145454545

 $00:05:18.298 \rightarrow 00:05:20.733$ variety of different genetic defects.

NOTE Confidence: 0.914410145454545

 $00:05:20.740 \longrightarrow 00:05:22.456$ But at least 50% of them,

NOTE Confidence: 0.914410145454545

 $00:05:22.460 \rightarrow 00:05:24.336$ we really don't know the underlying cause,

NOTE Confidence: 0.914410145454545

 $00:05:24.340 \longrightarrow 00:05:26.384$ although it's believed that

NOTE Confidence: 0.914410145454545

 $00:05:26.384 \rightarrow 00:05:28.939$ many of those are genetic.

NOTE Confidence: 0.914410145454545

 $00{:}05{:}28{.}940 \dashrightarrow 00{:}05{:}31{.}124$ And that's really where this is

NOTE Confidence: 0.914410145454545

 $00{:}05{:}31{.}124 \dashrightarrow 00{:}05{:}33{.}954$ led me to kind of start thinking

NOTE Confidence: 0.914410145454545

 $00{:}05{:}33{.}954 \dashrightarrow 00{:}05{:}36{.}540$ about this 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

 $00:05:39.004 \rightarrow 00:05:42.220$ invited to give a talk at a.

NOTE Confidence: 0.914410145454545

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

 $00:05:44.752 \rightarrow 00:05:47.370$ it's a type of syndrome that you

NOTE Confidence: 0.914410145454545

 $00:05:47.370 \longrightarrow 00:05:49.176$ see and at the time I, I,

NOTE Confidence: 0.914410145454545

 $00{:}05{:}49{.}176 \dashrightarrow 00{:}05{:}50{.}832$ I started looking and I asked

NOTE Confidence: 0.914410145454545

 $00:05:50.832 \rightarrow 00:05:52.220$ the question well how many,

NOTE Confidence: 0.914410145454545

 $00{:}05{:}52{.}220 \dashrightarrow 00{:}05{:}54{.}005$ what do we know about the genes

NOTE Confidence: 0.914410145454545

 $00{:}05{:}54.005 \dashrightarrow 00{:}05{:}55.761$ that are involved at that time And

NOTE Confidence: 0.914410145454545

 $00:05:55.761 \dashrightarrow 00:05:57.461$ this list is much longer but this

NOTE Confidence: 0.914410145454545

 $00{:}05{:}57{.}461 \dashrightarrow 00{:}05{:}59{.}388$ is where I started and at the

NOTE Confidence: 0.914410145454545

 $00:05:59.388 \rightarrow 00:06:00.840$ time there was just this relatively

NOTE Confidence: 0.914410145454545

 $00:06:00.889 \rightarrow 00:06:02.599$ small number of genes that are

NOTE Confidence: 0.914410145454545

 $00:06:02.599 \longrightarrow 00:06:03.986$ involved there's there's now at

NOTE Confidence: 0.914410145454545

 $00{:}06{:}03{.}986 \dashrightarrow 00{:}06{:}06{.}455$ least 152 genes involved in or

NOTE Confidence: 0.914410145454545

 $00{:}06{:}06{.}455 \dashrightarrow 00{:}06{:}08{.}972$ 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,

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

NOTE Confidence: 0.914410145454545

 $00:06:15.740 \longrightarrow 00:06:19.844$ kind of analysis and I was able to kind

NOTE Confidence: 0.914410145454545

 $00:06:19.844 \rightarrow 00:06:23.939$ of orc or divide them up into nuclear genes,

NOTE Confidence: 0.914410145454545

 $00:06:23.940 \rightarrow 00:06:26.139$ membrane associated genes.

NOTE Confidence: 0.914410145454545

 $00:06:26.139 \longrightarrow 00:06:29.800$ 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

 $00:06:38.830 \longrightarrow 00:06:40.730$ disease genes came up.

NOTE Confidence: 0.914410145454545

 $00:06:40.730 \dashrightarrow 00:06:42.737$ And So what I'm going to do today is

NOTE Confidence: 0.914410145454545

 $00:06:42.737 \rightarrow 00:06:44.945$ take you through two of these because

NOTE Confidence: 0.914410145454545

 $00:06:44.945 \rightarrow 00:06:46.545$ 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

 $00:06:48.850 \rightarrow 00:06:50.752$ the first one in that line,

NOTE Confidence: 0.914410145454545

 $00:06:50.752 \longrightarrow 00:06:52.564$ for quite a bit of time.

00:06:52.570 --> 00:06:54.089 And then I'm going to switch over

NOTE Confidence: 0.914410145454545

 $00:06:54.089 \rightarrow 00:06:55.924$ and tell you a little bit about

NOTE Confidence: 0.914410145454545

 $00{:}06{:}55{.}924 \dashrightarrow 00{:}06{:}57{.}339$ mitochondrial ones and how those

NOTE Confidence: 0.914410145454545

 $00:06:57.339 \rightarrow 00:06:58.996$ actually came together in thinking

NOTE Confidence: 0.914410145454545

 $00{:}06{:}58.996 \dashrightarrow 00{:}07{:}00.408$ 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

 $00:07:04.898 \rightarrow 00:07:07.978$ started, just to remind everyone about the

NOTE Confidence: 0.936228169

 $00:07:07.978 \rightarrow 00:07:10.130$ 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

 $00:07:11.090 \longrightarrow 00:07:13.650$ 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

 $00:07:14.770 \longrightarrow 00:07:16.758$ yeah, so layer one of the cortex

NOTE Confidence: 0.936228169

 $00:07:16.758 \rightarrow 00:07:18.968$ 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

 $00{:}07{:}20.400 \dashrightarrow 00{:}07{:}21.378$ brain during development.

 $00:07:21.378 \rightarrow 00:07:22.410$ 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

 $00:07:24.475 \longrightarrow 00:07:26.485$ 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

 $00:07:30.042 \longrightarrow 00:07:31.580$ organization of the sixth layer,

NOTE Confidence: 0.936228169

 $00{:}07{:}31.580 \dashrightarrow 00{:}07{:}34.345$ the laminar cortex layer two is known

NOTE Confidence: 0.936228169

 $00:07:34.345 \rightarrow 00:07:37.099$ as the external granular cell layer.

NOTE Confidence: 0.936228169

 $00{:}07{:}37{.}100 \dashrightarrow 00{:}07{:}39{.}858$ 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

 $00{:}07{:}44.308 \dashrightarrow 00{:}07{:}47.480$ three is the external pyramidal cell layer.

NOTE Confidence: 0.936228169

 $00:07:47.480 \longrightarrow 00:07:51.113$ Now I want to take this moment to say

NOTE Confidence: 0.936228169

 $00{:}07{:}51{.}113 \dashrightarrow 00{:}07{:}53{.}738$ that all layers have both excited to

NOTE Confidence: 0.936228169

 $00:07:53.740 \dashrightarrow 00:07:56.220$ have pyramidal and granular neurons.

NOTE Confidence: 0.936228169

 $00:07:56.220 \rightarrow 00:07:58.326$ It's just the relative distribution that

NOTE Confidence: 0.936228169

 $00:07:58.326 \rightarrow 00:08:00.966$ 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
- $00:08:02.964 \longrightarrow 00:08:04.536$ a paramidal cell layer.
- NOTE Confidence: 0.936228169
- $00:08:04.536 \rightarrow 00:08:07.888$ So we have an external paramidal cell layer,
- NOTE Confidence: 0.936228169
- $00:08:07.888 \longrightarrow 00:08:08.824$ layer 3.
- NOTE Confidence: 0.936228169
- $00:08:08.824 \rightarrow 00:08:11.580$ Then you have a internal granular
- NOTE Confidence: 0.936228169
- $00:08:11.580 \longrightarrow 00:08:14.220$ 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
- $00:08:15.860 \dashrightarrow 00:08:17.500$ the different cortical regions.
- NOTE Confidence: 0.936228169
- $00:08:17.500 \longrightarrow 00:08:18.148$ 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
- $00:08:19.660 \rightarrow 00:08:21.180$ this is from motor cortex,
- NOTE Confidence: 0.936228169
- $00{:}08{:}21{.}180 \dashrightarrow 00{:}08{:}23{.}140$ if you look at the visual cortex.
- NOTE Confidence: 0.936228169
- $00:08:23.140 \rightarrow 00:08:25.390$ Layer 4 is dramatically expanded and
- NOTE Confidence: 0.936228169
- $00:08:25.390 \rightarrow 00:08:28.138$ it's the major input from the thalamus,
- NOTE Confidence: 0.936228169
- $00:08:28.140 \dashrightarrow 00:08:30.744$ whereas in the motor cortex there's
- NOTE Confidence: 0.936228169

 $00:08:30.744 \longrightarrow 00:08:33.099$ 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: 0.924419793333333

 $00:08:39.220 \rightarrow 00:08:40.952$ output pyramidal cell layer,

NOTE Confidence: 0.924419793333333

 $00:08:40.952 \longrightarrow 00:08:42.280$ that goes, for example,

NOTE Confidence: 0.924419793333333

 $00{:}08{:}42.280 \dashrightarrow 00{:}08{:}43.660$ the large bed cells that go

NOTE Confidence: 0.924419793333333

 $00:08:43.660 \longrightarrow 00:08:44.940$ down in the spinal cord,

NOTE Confidence: 0.924419793333333

 $00:08:44.940 \longrightarrow 00:08:47.220$ those are all in layer 5.

NOTE Confidence: 0.924419793333333

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

NOTE Confidence: 0.924419793333333

 $00:08:48.860 \rightarrow 00:08:50.210$ including to the other side

NOTE Confidence: 0.924419793333333

 $00:08:50.210 \longrightarrow 00:08:52.744$ of the brain and then layer 6.

NOTE Confidence: 0.924419793333333

 $00:08:52.744 \longrightarrow 00:08:55.330$ Which is against the white matter.

NOTE Confidence: 0.924419793333333

 $00{:}08{:}55{.}330 \dashrightarrow 00{:}08{:}57{.}738$ This is the what's known as the multiform

NOTE Confidence: 0.924419793333333

 $00:08:57.738 \dashrightarrow 00:08:59.673$ or fusiform layer and it consists

NOTE Confidence: 0.924419793333333

 $00:08:59.673 \dashrightarrow 00:09:01.581$ of a variety of different neuronal

NOTE Confidence: 0.924419793333333

 $00:09:01.643 \rightarrow 00:09:03.687$ types and has both input and output.

 $00:09:03.690 \longrightarrow 00:09:06.050$ And then below that is the white matter.

NOTE Confidence: 0.924419793333333

 $00:09:06.050 \rightarrow 00:09:08.490$ So that's the six layers of the cortex.

NOTE Confidence: 0.924419793333333

00:09:08.490 --> 00:09:11.010 And these layers are composed,

NOTE Confidence: 0.924419793333333

 $00:09:11.010 \rightarrow 00:09:13.650$ as I said of these granular neurons,

NOTE Confidence: 0.924419793333333

 $00:09:13.650 \rightarrow 00:09:17.094$ here labeled non spining neurons and the

NOTE Confidence: 0.924419793333333

 $00:09:17.094 \rightarrow 00:09:20.724$ spining neurons or the pyramidal cells now.

NOTE Confidence: 0.924419793333333

 $00:09:20.724 \rightarrow 00:09:23.568$ These two cell types compose the

NOTE Confidence: 0.924419793333333

 $00:09:23.570 \rightarrow 00:09:25.845$ major 2 cell types in the cortex,

NOTE Confidence: 0.924419793333333

 $00:09:25.850 \longrightarrow 00:09:26.960$ the excitatory neurons,

NOTE Confidence: 0.924419793333333

 $00:09:26.960 \longrightarrow 00:09:28.810$ those are the spiny ones,

NOTE Confidence: 0.924419793333333

 $00:09:28.810 \rightarrow 00:09:31.090$ they use glutamate as a neurotransmitter,

NOTE Confidence: 0.924419793333333

00:09:31.090 - > 00:09:34.548 and the non spiny or the inhibitory

NOTE Confidence: 0.924419793333333

 $00:09:34.548 \dashrightarrow 00:09:36.890$ interneurons which all use GABA.

NOTE Confidence: 0.924419793333333

 $00:09:36.890 \longrightarrow 00:09:37.928$ But as you can see here,

NOTE Confidence: 0.924419793333333

 $00:09:37.930 \rightarrow 00:09:39.315$ there's actually many different forms

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

NOTE Confidence: 0.924419793333333

 $00:09:41.090 \longrightarrow 00:09:41.732$ and there's.

NOTE Confidence: 0.924419793333333

 $00:09:41.732 \longrightarrow 00:09:44.300$ Probably on the order of 30 to 40

NOTE Confidence: 0.924419793333333

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

NOTE Confidence: 0.924419793333333

 $00{:}09{:}46{.}465 \dashrightarrow 00{:}09{:}49{.}407$ and in the order of 60 of different

NOTE Confidence: 0.924419793333333

 $00:09:49.407 \longrightarrow 00:09:51.252$ types of inhibitory neurons or

NOTE Confidence: 0.924419793333333

 $00:09:51.252 \rightarrow 00:09:55.350$ the these non spiny interneurons.

NOTE Confidence: 0.924419793333333

 $00:09:55.350 \rightarrow 00:09:58.994$ Normal cortical development requires

NOTE Confidence: 0.924419793333333

 $00:09:58.994 \longrightarrow 00:10:03.338$ an integration of both of these

NOTE Confidence: 0.924419793333333

 $00:10:03.338 \rightarrow 00:10:05.510$ types of neurons.

NOTE Confidence: 0.924419793333333

 $00{:}10{:}05{.}510 \dashrightarrow 00{:}10{:}07{.}568$ If you don't have the excitatory

NOTE Confidence: 0.924419793333333

 $00{:}10{:}07.568 \dashrightarrow 00{:}10{:}09.785$ neurons and the inhibitory neurons you

NOTE Confidence: 0.924419793333333

 $00:10:09.785 \rightarrow 00:10:11.740$ get disruptions in normal cortical.

NOTE Confidence: 0.924419793333333

00:10:11.740 --> 00:10:12.282 Functions,

NOTE Confidence: 0.924419793333333

 $00{:}10{:}12.282 \dashrightarrow 00{:}10{:}14.992$ circuits that result in functional

NOTE Confidence: 0.924419793333333

 $00:10:14.992 \longrightarrow 00:10:18.048$ defects and those give rise to a

00:10:18.048 --> 00:10:20.500 variety of different developmental disorders.

NOTE Confidence: 0.924419793333333

 $00:10:20.500 \longrightarrow 00:10:22.756$ And what you can see here is the

NOTE Confidence: 0.924419793333333

 $00:10:22.756 \rightarrow 00:10:24.624$ different types of excitatory and

NOTE Confidence: 0.924419793333333

 $00:10:24.624 \rightarrow 00:10:27.096$ inhibitory neurons connect in different ways.

NOTE Confidence: 0.924419793333333

 $00{:}10{:}27{.}100 \dashrightarrow 00{:}10{:}29{.}062$ So there are some inhibitory neurons

NOTE Confidence: 0.924419793333333

 $00:10:29.062 \rightarrow 00:10:31.304$ like this green one that predominantly

NOTE Confidence: 0.924419793333333

 $00:10:31.304 \rightarrow 00:10:34.325$ function by connecting on the Axon and

NOTE Confidence: 0.924419793333333

00:10:34.325 --> 00:10:37.379 the proximal Axon and the cell body,

NOTE Confidence: 0.924419793333333

 $00:10:37.380 \longrightarrow 00:10:39.230$ whereas others are going to

NOTE Confidence: 0.924419793333333

 $00:10:39.230 \longrightarrow 00:10:40.710$ connect more on dendrites.

NOTE Confidence: 0.924419793333333

00:10:40.710 --> 00:10:43.310 And some just on the cell body itself,

NOTE Confidence: 0.924419793333333

 $00:10:43.310 \longrightarrow 00:10:45.042$ like this purple one.

NOTE Confidence: 0.924419793333333

 $00:10:45.042 \rightarrow 00:10:48.364$ And these are all required to appropriately

NOTE Confidence: 0.924419793333333

 $00{:}10{:}48.364 \dashrightarrow 00{:}10{:}51.549$ modulate circuits in the brain.

NOTE Confidence: 0.924419793333333

 $00{:}10{:}51{.}550 \dashrightarrow 00{:}10{:}53{.}692$ So you need all these different types

 $00:10:53.692 \rightarrow 00:10:55.635$ to get the appropriate development

NOTE Confidence: 0.924419793333333

 $00{:}10{:}55{.}635 \dashrightarrow 00{:}10{:}58{.}503$ and function of the cerebral cortex.

NOTE Confidence: 0.917191383333333

 $00{:}11{:}01{.}590 \dashrightarrow 00{:}11{:}04{.}020$ Well, what's interesting also about this

NOTE Confidence: 0.917191383333333

 $00:11:04.020 \rightarrow 00:11:07.338$ is that these two different neuronal types

NOTE Confidence: 0.917191383333333

 $00{:}11{:}07{.}338$ --> $00{:}11{:}10{.}043$ come from different progenitor zones.

NOTE Confidence: 0.917191383333333

 $00:11:10.050 \rightarrow 00:11:14.210$ Now in the for the cortical excitatory

NOTE Confidence: 0.917191383333333

 $00:11:14.210 \longrightarrow 00:11:16.302$ neurons, they are essentially

NOTE Confidence: 0.917191383333333

 $00:11:16.302 \longrightarrow 00:11:18.486$ all driven from or derived from

NOTE Confidence: 0.917191383333333

 $00{:}11{:}18.486 \dashrightarrow 00{:}11{:}20.610$ the cortical ventricular zone,

NOTE Confidence: 0.917191383333333

 $00{:}11{:}20.610 \dashrightarrow 00{:}11{:}23.352$ that dorsal portion of progenitor cells

NOTE Confidence: 0.917191383333333

 $00{:}11{:}23.352 \dashrightarrow 00{:}11{:}26.790$ that are along the ventricle and these

NOTE Confidence: 0.917191383333333

 $00{:}11{:}26.790 \dashrightarrow 00{:}11{:}29.250$ cells divide and they migrate out.

NOTE Confidence: 0.917191383333333

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

NOTE Confidence: 0.917191383333333

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

NOTE Confidence: 0.917191383333333

 $00:11:33.202 \longrightarrow 00:11:34.737$ here in the front row.

NOTE Confidence: 0.917191383333333

 $00{:}11{:}34{.}740 \dashrightarrow 00{:}11{:}37{.}220$ Has shown that these cells migrate out the

 $00:11:37.220 \rightarrow 00:11:39.655$ first form of what's called a preplate A,

NOTE Confidence: 0.917191383333333

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

NOTE Confidence: 0.917191383333333

 $00:11:40.832 \longrightarrow 00:11:42.297$ and then a subplate neuron,

NOTE Confidence: 0.917191383333333

 $00:11:42.300 \longrightarrow 00:11:45.420$ which is really important for the

NOTE Confidence: 0.917191383333333

 $00{:}11{:}45{.}420 \dashrightarrow 00{:}11{:}48{.}284$ ultimate connection between the thalamic

NOTE Confidence: 0.917191383333333

 $00{:}11{:}48.284 \dashrightarrow 00{:}11{:}51.214$ nuclei and the cortical region.

NOTE Confidence: 0.917191383333333

 $00:11:51.220 \rightarrow 00:11:52.480$ So defining, for example,

NOTE Confidence: 0.917191383333333

 $00:11:52.480 \longrightarrow 00:11:54.370$ the visual cortex in the lateral

NOTE Confidence: 0.917191383333333

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

NOTE Confidence: 0.917191383333333

 $00:11:55.300 \rightarrow 00:11:56.818$ For those connections to be made,

NOTE Confidence: 0.917191383333333

 $00:11:56.820 \longrightarrow 00:11:59.380$ it requires those subplate neurons.

NOTE Confidence: 0.917191383333333

 $00{:}11{:}59{.}380 \dashrightarrow 00{:}12{:}01{.}718$ They that the call ritzius neuron and

NOTE Confidence: 0.917191383333333

 $00{:}12{:}01{.}718 \dashrightarrow 00{:}12{:}03{.}610$ the subplate neuron are important.

NOTE Confidence: 0.917191383333333

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

NOTE Confidence: 0.917191383333333

 $00:12:06.410 \longrightarrow 00:12:07.530$ definitive cortex,

 $00:12:07.530 \longrightarrow 00:12:10.050$ that layer 2 through 6.

NOTE Confidence: 0.917191383333333

 $00:12:10.050 \rightarrow 00:12:12.276$ Fill in between those and they fill

NOTE Confidence: 0.917191383333333

 $00:12:12.276 \longrightarrow 00:12:15.078$ in in an inverse pattern from the

NOTE Confidence: 0.917191383333333

 $00:12:15.078 \rightarrow 00:12:17.730$ deep layer to the superficial layer.

NOTE Confidence: 0.917191383333333

00:12:17.730 --> 00:12:18.660 In mice,

NOTE Confidence: 0.917191383333333

 $00:12:18.660 \longrightarrow 00:12:20.985$ all of the excitatory neurons

NOTE Confidence: 0.917191383333333

 $00:12:20.985 \longrightarrow 00:12:23.090$ come from this region,

NOTE Confidence: 0.917191383333333

 $00:12:23.090 \rightarrow 00:12:25.407$ and it looks like in humans too,

NOTE Confidence: 0.917191383333333

 $00{:}12{:}25{.}410 \dashrightarrow 00{:}12{:}25{.}998$ inhibitory neurons,

NOTE Confidence: 0.917191383333333

 $00{:}12{:}25{.}998 \dashrightarrow 00{:}12{:}28{.}350$ which I'll show you on the next slide.

NOTE Confidence: 0.917191383333333

 $00:12:28.350 \longrightarrow 00:12:30.401$ There may be some that are derived

NOTE Confidence: 0.917191383333333

 $00{:}12{:}30{.}401 \dashrightarrow 00{:}12{:}32{.}205$ from the ventricular zone in

NOTE Confidence: 0.917191383333333

 $00:12:32.205 \longrightarrow 00:12:34.404$ the in the human dorsal cortex,

NOTE Confidence: 0.917191383333333

 $00{:}12{:}34{.}404 \dashrightarrow 00{:}12{:}37{.}389$ but it does not appear to be in the mouse.

NOTE Confidence: 0.917191383333333

 $00:12:37.390 \longrightarrow 00:12:40.267$ In the human and in the mouse,

NOTE Confidence: 0.917191383333333

 $00:12:40.270 \rightarrow 00:12:41.884$ the vast majority are from another

- NOTE Confidence: 0.917191383333333
- $00:12:41.884 \rightarrow 00:12:43.629$ progenitor region and I'll show you that.
- NOTE Confidence: 0.917191383333333
- $00{:}12{:}43.630 \dashrightarrow 00{:}12{:}45.830$ Next I do want to just briefly mention,
- NOTE Confidence: 0.917191383333333
- $00:12:45.830 \rightarrow 00:12:47.104$ because I'm going to talk about it,
- NOTE Confidence: 0.917191383333333
- $00:12:47.110 \longrightarrow 00:12:48.870$ there's an intermediate progenitor zone.
- NOTE Confidence: 0.917191383333333
- $00{:}12{:}48.870 \dashrightarrow 00{:}12{:}51.030$ This is called the sub ventricular
- NOTE Confidence: 0.917191383333333
- $00:12:51.030 \longrightarrow 00:12:53.910$ zone and this is where cells.
- NOTE Confidence: 0.917191383333333
- $00:12:53.910 \rightarrow 00:12:55.970$ Actually go from the ventricular
- NOTE Confidence: 0.917191383333333
- $00:12:55.970 \longrightarrow 00:12:58.630$ zone being a stem cell to this
- NOTE Confidence: 0.917191383333333
- $00:12:58.630 \rightarrow 00:13:01.205$ this subventricular zone where they
- NOTE Confidence: 0.917191383333333
- $00:13:01.205 \rightarrow 00:13:03.265$ form an intermediate progenitor.
- NOTE Confidence: 0.917191383333333
- $00:13:03.270 \rightarrow 00:13:05.820$ Go through one or several divisions
- NOTE Confidence: 0.917191383333333
- $00:13:05.820 \rightarrow 00:13:07.682$ before ultimately and exiting the cell
- NOTE Confidence: 0.917191383333333
- $00{:}13{:}07.682 \dashrightarrow 00{:}13{:}09.630$ cycle and going up into the cortex.
- NOTE Confidence: 0.905435112
- $00:13:13.030 \dashrightarrow 00:13:16.350$ Now this, this is the what I was showing you.
- NOTE Confidence: 0.905435112
- $00{:}13{:}16{.}350 \dashrightarrow 00{:}13{:}18{.}667$ Here's the this is a hemi section.
- NOTE Confidence: 0.905435112

- $00:13:18.670 \longrightarrow 00:13:20.650$ Imagine this being a hemi
- NOTE Confidence: 0.905435112
- $00{:}13{:}20.650 \dashrightarrow 00{:}13{:}22.234$ section through the brain.
- NOTE Confidence: 0.905435112
- $00:13:22.240 \longrightarrow 00:13:24.354$ And it could be any mammalian species.
- NOTE Confidence: 0.905435112
- $00:13:24.360 \longrightarrow 00:13:26.152$ And it's one side.
- NOTE Confidence: 0.905435112
- $00:13:26.152 \longrightarrow 00:13:28.392$ So this is the midline,
- NOTE Confidence: 0.905435112
- $00:13:28.400 \rightarrow 00:13:31.438$ this is dorsal or the top, this is ventral,
- NOTE Confidence: 0.905435112
- $00:13:31.438 \longrightarrow 00:13:33.274$ the bottom and this is lateral.
- NOTE Confidence: 0.905435112
- $00{:}13{:}33{.}280 \dashrightarrow 00{:}13{:}34{.}184$ The cortical ventricular zone
- NOTE Confidence: 0.905435112
- $00:13:34.184 \longrightarrow 00:13:35.314$ that I've been talking about,
- NOTE Confidence: 0.905435112
- $00:13:35.320 \rightarrow 00:13:36.490$ where the excitatory
- NOTE Confidence: 0.905435112
- $00{:}13{:}36{.}490 \dashrightarrow 00{:}13{:}38{.}440$ neurons come from is here.
- NOTE Confidence: 0.905435112
- $00:13:38.440 \longrightarrow 00:13:40.135$ And then there's this structure
- NOTE Confidence: 0.905435112
- $00:13:40.135 \rightarrow 00:13:41.830$ known as the ganglionic eminence
- NOTE Confidence: 0.905435112
- $00:13:41.889 \longrightarrow 00:13:43.639$ in the ventral part of the brain.
- NOTE Confidence: 0.905435112
- $00:13:43.640 \longrightarrow 00:13:45.105$ This is where these inhibitory
- NOTE Confidence: 0.905435112
- $00:13:45.105 \rightarrow 00:13:46.277$ neurons are derived from.

- NOTE Confidence: 0.905435112
- $00:13:46.280 \rightarrow 00:13:49.936$ And what's interesting is that if you look.

 $00:13:49.940 \longrightarrow 00:13:50.888$ Along the dorsal,

NOTE Confidence: 0.905435112

 $00:13:50.888 \rightarrow 00:13:53.504$ ventral axis from the neural at the beginning

NOTE Confidence: 0.905435112

 $00:13:53.504 \rightarrow 00:13:56.256$ of the nervous system in this neural tube,

NOTE Confidence: 0.905435112

 $00:13:56.260 \longrightarrow 00:13:57.892$ from dorsal to ventral,

NOTE Confidence: 0.905435112

 $00:13:57.892 \rightarrow 00:14:00.636$ you get different neural types defined

NOTE Confidence: 0.905435112

 $00:14:00.636 \rightarrow 00:14:03.420$ by different genetic pathways.

NOTE Confidence: 0.905435112

 $00{:}14{:}03.420 \dashrightarrow 00{:}14{:}05.820$ And you see that also in the forebrain.

NOTE Confidence: 0.905435112

 $00:14:05.820 \longrightarrow 00:14:07.136$ So this is in the spinal cord,

NOTE Confidence: 0.905435112

 $00:14:07.140 \longrightarrow 00:14:08.148$ but in the forebrain.

NOTE Confidence: 0.905435112

 $00{:}14{:}08{.}148 \dashrightarrow 00{:}14{:}09{.}660$ And there's specific genes that are

NOTE Confidence: 0.905435112

 $00{:}14{:}09{.}712 \dashrightarrow 00{:}14{:}11{.}042$ expressed in these different regions

NOTE Confidence: 0.905435112

 $00:14:11.042 \longrightarrow 00:14:12.763$ that give rise to these different

NOTE Confidence: 0.905435112

 $00{:}14{:}12.763 \dashrightarrow 00{:}14{:}14.498$ progenitors and different cell types.

NOTE Confidence: 0.905435112

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

 $00:14:14.844 \rightarrow 00:14:15.876$ I'm going to come back to

NOTE Confidence: 0.905435112

 $00{:}14{:}15.876 \dashrightarrow 00{:}14{:}16.740$ talk about that as well.

NOTE Confidence: 0.935781098888889

 $00:14:19.180 \longrightarrow 00:14:21.016$ So what does this look like in the human?

NOTE Confidence: 0.935781098888889

 $00:14:21.020 \longrightarrow 00:14:22.740$ So on your left side,

NOTE Confidence: 0.935781098888889

 $00:14:22.740 \longrightarrow 00:14:27.380$ that's a human about 7 1/2 weeks gestation.

NOTE Confidence: 0.935781098888889

 $00{:}14{:}27{.}380 \dashrightarrow 00{:}14{:}30{.}076$ And you can see the ganglionic eminence where

NOTE Confidence: 0.935781098888889

 $00:14:30.076 \rightarrow 00:14:32.012$ these inhibitory neurons are predominately

NOTE Confidence: 0.935781098888889

 $00{:}14{:}32.012 \dashrightarrow 00{:}14{:}34.017$ coming from the ventricular zone.

NOTE Confidence: 0.935781098888889

 $00{:}14{:}34{.}020 \dashrightarrow 00{:}14{:}36{.}334$ And this here is the preplate and

NOTE Confidence: 0.935781098888889

 $00:14:36.334 \rightarrow 00:14:37.738$ you can see the preplate forming,

NOTE Confidence: 0.935781098888889

 $00:14:37.740 \longrightarrow 00:14:39.072$ it's a little larger,

NOTE Confidence: 0.935781098888889

 $00{:}14{:}39{.}072 \dashrightarrow 00{:}14{:}41{.}540$ It actually starts in the ventrilateral

NOTE Confidence: 0.935781098888889

 $00:14:41.540 \rightarrow 00:14:45.292$ location and it moves. Moves up,

NOTE Confidence: 0.935781098888889

 $00{:}14{:}45{.}292 \dashrightarrow 00{:}14{:}47{.}860$ so it doesn't all develop at the same time.

NOTE Confidence: 0.935781098888889

 $00:14:47.860 \rightarrow 00:14:50.338$ It also goes from anterior to posterior,

NOTE Confidence: 0.935781098888889

 $00:14:50.340 \longrightarrow 00:14:51.828$ so you can see that in

- NOTE Confidence: 0.935781098888889
- $00:14:51.828 \longrightarrow 00:14:52.820$ the very dorsal regions,
- NOTE Confidence: 0.935781098888889
- $00{:}14{:}52{.}820 \dashrightarrow 00{:}14{:}54{.}296$ there's not even a preplate yet.
- NOTE Confidence: 0.935781098888889
- $00:14:54.300 \rightarrow 00:14:59.539$ At 7 1/2 weeks by 20 weeks,
- NOTE Confidence: 0.935781098888889
- $00:14:59.540 \longrightarrow 00:15:01.380$ the station which is here,
- NOTE Confidence: 0.935781098888889
- $00:15:01.380 \longrightarrow 00:15:02.540$ you can see the hippocampus.
- NOTE Confidence: 0.935781098888889
- $00{:}15{:}02.540 \dashrightarrow 00{:}15{:}04.220$ So we're looking at the temporal lobe,
- NOTE Confidence: 0.935781098888889
- $00:15:04.220 \longrightarrow 00:15:07.140$ and essentially all the neurons,
- NOTE Confidence: 0.935781098888889
- $00:15:07.140 \longrightarrow 00:15:08.640$ with a few exceptions,
- NOTE Confidence: 0.935781098888889
- $00{:}15{:}08.640 \dashrightarrow 00{:}15{:}10.515$ are already in the cortex.
- NOTE Confidence: 0.935781098888889
- $00:15:10.520 \rightarrow 00:15:11.820$ So they've migrated out,
- NOTE Confidence: 0.935781098888889
- $00:15:11.820 \rightarrow 00:15:13.520$ but they haven't yet differentiated
- NOTE Confidence: 0.935781098888889
- $00:15:13.520 \longrightarrow 00:15:15.120$ and defined themselves in
- NOTE Confidence: 0.935781098888889
- $00:15:15.120 \rightarrow 00:15:16.320$ different laminar organization,
- NOTE Confidence: 0.935781098888889
- $00{:}15{:}16{.}320 \dashrightarrow 00{:}15{:}17{.}260$ but they are molecularly
- NOTE Confidence: 0.935781098888889
- $00{:}15{:}17{.}260 \dashrightarrow 00{:}15{:}18{.}200$ defined by that time.
- NOTE Confidence: 0.935781098888889

00:15:18.200 --> 00:15:18.804 All right.

NOTE Confidence: 0.935781098888889

 $00{:}15{:}18{.}804 \dashrightarrow 00{:}15{:}21{.}320$ 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

 $00{:}15{:}23.720 \dashrightarrow 00{:}15{:}25.224$ to thinking about the studies

NOTE Confidence: 0.935781098888889

 $00:15:25.224 \rightarrow 00:15:26.880$ I'm going to tell you about.

NOTE Confidence: 0.935781098888889

 $00{:}15{:}26.880 \dashrightarrow 00{:}15{:}29.064$ I'm going to start out telling you

NOTE Confidence: 0.935781098888889

 $00{:}15{:}29.064 \dashrightarrow 00{:}15{:}30.370$ about that transcription factor

NOTE Confidence: 0.935781098888889

 $00:15:30.370 \rightarrow 00:15:31.984$ that is associated with epilepsy.

NOTE Confidence: 0.935781098888889

 $00{:}15{:}31{.}984 \dashrightarrow 00{:}15{:}33{.}360$ It's actually associated with

NOTE Confidence: 0.935781098888889

 $00{:}15{:}33{.}360 \dashrightarrow 00{:}15{:}35{.}520$ 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 Aristoless related homeobox gene,

NOTE Confidence: 0.935781098888889

 $00{:}15{:}38{.}560 \dashrightarrow 00{:}15{:}41{.}530$ so it's related to the Drosophila

NOTE Confidence: 0.935781098888889

 $00{:}15{:}41{.}530 \dashrightarrow 00{:}15{:}44{.}595$ ristolis gene and this gene is on

NOTE Confidence: 0.935781098888889

 $00{:}15{:}44{.}595 \dashrightarrow 00{:}15{:}47{.}564$ the X chromosome and in males what

NOTE Confidence: 0.935781098888889

 $00:15:47.564 \rightarrow 00:15:51.652$ you see is a spectrum of neurologic

- NOTE Confidence: 0.935781098888889
- $00{:}15{:}51.652 \dashrightarrow 00{:}15{:}53.712$ and cognitive deficits and and
- NOTE Confidence: 0.935781098888889
- $00{:}15{:}53{.}712 \dashrightarrow 00{:}15{:}56{.}709$ and I really was attracted to this
- NOTE Confidence: 0.935781098888889
- $00:15:56.709 \rightarrow 00:15:58.839$ gene because of this spectrum.
- NOTE Confidence: 0.935781098888889
- $00{:}15{:}58{.}840 \dashrightarrow 00{:}16{:}01{.}400$ So some mutations resulted in
- NOTE Confidence: 0.935781098888889
- $00:16:01.400 \rightarrow 00:16:04.770$ hydrocephalus and and abnormal genitalia.
- NOTE Confidence: 0.935781098888889
- $00:16:04.770 \longrightarrow 00:16:05.770$ That's a pretty rare one.
- NOTE Confidence: 0.935781098888889
- $00{:}16{:}05{.}770 \dashrightarrow 00{:}16{:}07{.}156$ What's most common was the second
- NOTE Confidence: 0.935781098888889
- $00:16:07.156 \rightarrow 00:16:09.770$ 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
- $00:16:14.250 \longrightarrow 00:16:15.720$ the corpus callosum.
- NOTE Confidence: 0.935781098888889
- $00{:}16{:}15{.}720 \dashrightarrow 00{:}16{:}18{.}170$ You could have infantile spasms.
- NOTE Confidence: 0.935781098888889
- $00{:}16{:}18{.}170 \dashrightarrow 00{:}16{:}19{.}654$ That was what I showed you in
- NOTE Confidence: 0.935781098888889
- $00{:}16{:}19.654 \dashrightarrow 00{:}16{:}20.290$ that child earlier.
- NOTE Confidence: 0.935781098888889
- $00{:}16{:}20.290 \dashrightarrow 00{:}16{:}22.570$ That does have an ARX mutation
- NOTE Confidence: 0.935781098888889

 $00:16:22.570 \longrightarrow 00:16:23.848$ and a variety of other things,

NOTE Confidence: 0.935781098888889

 $00{:}16{:}23.850 \dashrightarrow 00{:}16{:}26.330$ down to intellectual disabilities

NOTE Confidence: 0.935781098888889

 $00:16:26.330 \longrightarrow 00:16:27.570$ with seizures.

NOTE Confidence: 0.93622824

 $00{:}16{:}29{.}890 \dashrightarrow 00{:}16{:}31{.}522$ What I want to point out is that

NOTE Confidence: 0.93622824

 $00{:}16{:}31{.}522 \dashrightarrow 00{:}16{:}33{.}379$ 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

 $00:16:37.780 \longrightarrow 00:16:40.562$ callosum, and they have epilepsy

NOTE Confidence: 0.93622824

 $00{:}16{:}40.562 \dashrightarrow 00{:}16{:}42.326$ and intellectual disabilities.

NOTE Confidence: 0.93622824

 $00{:}16{:}42{.}330 \dashrightarrow 00{:}16{:}44{.}570$ At the bottom of the list are brains

NOTE Confidence: 0.93622824

 $00{:}16{:}44{.}570 \dashrightarrow 00{:}16{:}47{.}938$ that are structurally normal but

NOTE Confidence: 0.93622824

 $00{:}16{:}47.938 \dashrightarrow 00{:}16{:}49.978$ have the exact same intellectual

NOTE Confidence: 0.93622824

00:16:49.978 --> 00:16:51.202 disabilities and epilepsy,

NOTE Confidence: 0.93622824

 $00:16:51.210 \rightarrow 00:16:54.045$ presenting at almost the exact same time.

NOTE Confidence: 0.93622824

 $00:16:54.050 \rightarrow 00:16:55.324$ And this was really curious to me.

NOTE Confidence: 0.93622824

 $00:16:55.330 \rightarrow 00:16:58.018$ How can you have these two different?

- NOTE Confidence: 0.93622824
- $00:16:58.020 \longrightarrow 00:16:58.875$ Kind of phenotypes,

 $00:16:58.875 \rightarrow 00:17:00.300$ one with a structurally abnormal

NOTE Confidence: 0.93622824

 $00:17:00.300 \longrightarrow 00:17:02.017$ brain and one with a normal brain,

NOTE Confidence: 0.93622824

 $00:17:02.020 \rightarrow 00:17:05.380$ what's structurally normal based on MRI

NOTE Confidence: 0.93622824

 $00:17:05.380 \longrightarrow 00:17:09.778$ and have the same neurologic presentation.

NOTE Confidence: 0.93622824

 $00{:}17{:}09.780 \dashrightarrow 00{:}17{:}11.684$ And I want to try and address that

NOTE Confidence: 0.93622824

 $00{:}17{:}11.684 \dashrightarrow 00{:}17{:}13.848$ and I hope by the end of today I

NOTE Confidence: 0.93622824

 $00{:}17{:}13.848 \dashrightarrow 00{:}17{:}15.977$ 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

 $00{:}17{:}17{.}708 \dashrightarrow 00{:}17{:}19{.}979$ 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

 $00:17:21.740 \longrightarrow 00:17:23.188$ otherwise they were normal.

NOTE Confidence: 0.93622824

 $00:17:23.188 \longrightarrow 00:17:24.998$ We have shown in publications

NOTE Confidence: 0.93622824

 $00{:}17{:}24.998 \dashrightarrow 00{:}17{:}26.880$ that that's actually not true.

NOTE Confidence: 0.93622824

 $00{:}17{:}26.880 \dashrightarrow 00{:}17{:}28.320$ I'm not going to talk about females today,

 $00:17:28.320 \rightarrow 00:17:31.122$ but I'm happy to talk if you want to at the

NOTE Confidence: 0.93622824

 $00:17:31.122 \rightarrow 00:17:33.754$ end about the genetics and how that happens.

NOTE Confidence: 0.93622824

 $00{:}17{:}33.760 \dashrightarrow 00{:}17{:}34.960$ So let's talk about a RX.

NOTE Confidence: 0.93622824

 $00:17:34.960 \longrightarrow 00:17:37.636$ 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

 $00{:}17{:}38{.}912 \dashrightarrow 00{:}17{:}41{.}880$ the 2nd exon at the very end.

NOTE Confidence: 0.93622824

 $00{:}17{:}41.880 \dashrightarrow 00{:}17{:}42.908$ The second exon's the

NOTE Confidence: 0.93622824

 $00:17:42.908 \rightarrow 00:17:44.193$ largest at the very end.

NOTE Confidence: 0.93622824

 $00{:}17{:}44.200 \dashrightarrow 00{:}17{:}47.040$ 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

 $00{:}17{:}48.657 \dashrightarrow 00{:}17{:}52.210$ So it's got a paired like homeo domain.

NOTE Confidence: 0.93622824

 $00:17:52.210 \longrightarrow 00:17:53.645$ It's at the end of the second,

NOTE Confidence: 0.93622824

 $00:17:53.650 \longrightarrow 00:17:55.702$ going through the 3rd and into

NOTE Confidence: 0.93622824

 $00:17:55.702 \rightarrow 00:17:57.809$ the beginning of the 4th exons,

NOTE Confidence: 0.93622824

 $00{:}17{:}57{.}810 \dashrightarrow 00{:}17{:}59{.}610$ but I also and and and.

NOTE Confidence: 0.93622824

 $00:17:59.610 \longrightarrow 00:18:01.535$ So mutations at the top of that

- NOTE Confidence: 0.93622824
- $00:18:01.535 \rightarrow 00:18:03.528$ which are frame shift or deletions,
- NOTE Confidence: 0.93622824
- $00:18:03.530 \longrightarrow 00:18:05.430$ 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
- $00:18:07.330 \longrightarrow 00:18:10.658$ including the lizence phaly and
- NOTE Confidence: 0.93622824
- $00{:}18{:}10.658 \dashrightarrow 00{:}18{:}13.890$ the agents of the corpus callosum.
- NOTE Confidence: 0.93622824
- $00:18:13.890 \longrightarrow 00:18:16.795$ But at the bottom, I'm not sure.
- NOTE Confidence: 0.93622824
- $00:18:16.800 \rightarrow 00:18:19.040$ Why the lettering didn't come out right,
- NOTE Confidence: 0.93622824
- $00:18:19.040 \longrightarrow 00:18:22.491$ but it's at the bottom are some
- NOTE Confidence: 0.93622824
- $00{:}18{:}22{.}491 \dashrightarrow 00{:}18{:}24{.}592$ 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
- $00:18:27.262 \longrightarrow 00:18:30.140$ conserved amino acids and also
- NOTE Confidence: 0.93622824
- $00{:}18{:}30{.}140 \dashrightarrow 00{:}18{:}32{.}480$ these alanine tract expansion.
- NOTE Confidence: 0.93622824
- $00{:}18{:}32{.}480 \dashrightarrow 00{:}18{:}35{.}600$ 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
- $00:18:39.275 \rightarrow 00:18:40.199$ about these alanine tracts,
- NOTE Confidence: 0.949198762222222

 $00{:}18{:}40{.}200 \dashrightarrow 00{:}18{:}42{.}795$ but we now know that there's about 450

NOTE Confidence: 0.949198762222222

 $00{:}18{:}42.795 \dashrightarrow 00{:}18{:}44.925$ annotated genes in the human genome

NOTE Confidence: 0.949198762222222

 $00{:}18{:}44{.}925 \dashrightarrow 00{:}18{:}47{.}558$ that have an alanine tract in them.

NOTE Confidence: 0.949198762222222

 $00:18:47.560 \longrightarrow 00:18:49.360$ 75% of those are transcription factors.

NOTE Confidence: 0.949198762222222

 $00{:}18{:}49{.}360 \dashrightarrow 00{:}18{:}51{.}352$ So we think that it has something to

NOTE Confidence: 0.949198762222222

 $00{:}18{:}51{.}352 \dashrightarrow 00{:}18{:}53{.}440$ do with transcriptional regulation.

NOTE Confidence: 0.949198762222222

 $00:18:53.440 \longrightarrow 00:18:58.515$ And there's now 9 or 10 genes that

NOTE Confidence: 0.949198762222222

 $00{:}18{:}58{.}515 \dashrightarrow 00{:}19{:}01{.}400$ have an alanine tract expansion

NOTE Confidence: 0.949198762222222

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

NOTE Confidence: 0.949198762222222

 $00{:}19{:}04.528 \dashrightarrow 00{:}19{:}06.320$ expansions like Huntington's disease,

NOTE Confidence: 0.949198762222222

 $00{:}19{:}06{.}320 \dashrightarrow 00{:}19{:}09{.}519$ Kennedy syndrome, some of the HS P's,

NOTE Confidence: 0.94383830444445

 $00{:}19{:}11.600 \dashrightarrow 00{:}19{:}13.765$ those expansions in a lanine tracts

NOTE Confidence: 0.943838304444445

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

NOTE Confidence: 0.94383830444445

 $00{:}19{:}15{.}500 \dashrightarrow 00{:}19{:}18{.}140$ On the order of three to

NOTE Confidence: 0.94383830444445

 $00{:}19{:}18{.}140 \dashrightarrow 00{:}19{:}19{.}460$ 10 additional alanines.

NOTE Confidence: 0.94383830444445

 $00:19:19.460 \longrightarrow 00:19:21.692$ And unlike the Huntington's disease and

 $00:19:21.692 \rightarrow 00:19:24.636$ some of the others that show anticipation

NOTE Confidence: 0.94383830444445

 $00:19:24.636 \rightarrow 00:19:27.414$ with very long glutamine tract expansions,

NOTE Confidence: 0.94383830444445

 $00:19:27.420 \longrightarrow 00:19:30.885$ these are very short and they're all

NOTE Confidence: 0.94383830444445

00:19:30.885 --> 00:19:33.951 developmental, they're not neurodegenerative,

NOTE Confidence: 0.94383830444445

 $00:19:33.951 \rightarrow 00:19:37.379$ these are neurodevelopmental disorders.

NOTE Confidence: 0.94383830444445

 $00:19:37.380 \longrightarrow 00:19:39.802$ So we were quite curious about them

NOTE Confidence: 0.94383830444445

 $00:19:39.802 \rightarrow 00:19:43.020$ because these give rise to the same.

NOTE Confidence: 0.94383830444445

00:19:43.020 --> 00:19:45.180 Intellectual disabilities and epilepsy,

NOTE Confidence: 0.94383830444445

 $00:19:45.180 \longrightarrow 00:19:47.830$ but structurally normal brains and

NOTE Confidence: 0.94383830444445

 $00:19:47.830 \rightarrow 00:19:51.260$ I'll be telling you about that today.

NOTE Confidence: 0.94383830444445

 $00:19:51.260 \rightarrow 00:19:53.696$ So where is a RX expressed?

NOTE Confidence: 0.94383830444445

 $00{:}19{:}53.700 \dashrightarrow 00{:}19{:}57.161$ Well, work from John Rubenstein's lab out

NOTE Confidence: 0.94383830444445

 $00{:}19{:}57{.}161 \dashrightarrow 00{:}19{:}58{.}988$ in San Francisco showed that it's expressed

NOTE Confidence: 0.94383830444445

 $00:19:58.988 \rightarrow 00:20:00.820$ early on in the ganglionic eminence.

NOTE Confidence: 0.94383830444445

 $00:20:00.820 \longrightarrow 00:20:03.578$ Here you can see by insight to

 $00:20:03.578 \longrightarrow 00:20:05.499$ hybridization and throughout the cortex

NOTE Confidence: 0.94383830444445

 $00:20:05.500 \rightarrow 00:20:08.013$ and here we did an immunohistic chemistry

NOTE Confidence: 0.94383830444445

 $00:20:08.013 \rightarrow 00:20:10.268$ with an antibody that we developed.

NOTE Confidence: 0.94383830444445

 $00:20:10.270 \rightarrow 00:20:11.894$ And you can see that it's expressed

NOTE Confidence: 0.94383830444445

 $00{:}20{:}11.894 \dashrightarrow 00{:}20{:}13.510$ strongly in the ganglionic eminence as

NOTE Confidence: 0.94383830444445

 $00{:}20{:}13.510$ --> $00{:}20{:}15.547$ 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: 0.94383830444445

 $00:20:17.950 \rightarrow 00:20:19.990$ it's only expressed in a subset of cells,

NOTE Confidence: 0.94383830444445

 $00{:}20{:}19{.}990 \dashrightarrow 00{:}20{:}22{.}062$ And this was the first clue that it

NOTE Confidence: 0.94383830444445

 $00:20:22.062 \rightarrow 00:20:24.318$ may be different in the inhibitory

NOTE Confidence: 0.94383830444445

 $00:20:24.318 \longrightarrow 00:20:25.986$ in the excitatory neurons.

NOTE Confidence: 0.94383830444445

 $00{:}20{:}25{.}990 \dashrightarrow 00{:}20{:}28{.}915$ And it turns out that ARX is expressed in

NOTE Confidence: 0.94383830444445

 $00{:}20{:}28{.}915 \dashrightarrow 00{:}20{:}32{.}064$ all of the ventricular zone of the cortex,

NOTE Confidence: 0.94383830444445

 $00:20:32.070 \longrightarrow 00:20:34.222$ but it turns off as soon as those

NOTE Confidence: 0.94383830444445

 $00:20:34.222 \rightarrow 00:20:35.748$ cells exit the cell cycle.

NOTE Confidence: 0.94383830444445

 $00:20:35.750 \rightarrow 00:20:36.103$ However,

 $00{:}20{:}36.103 \dashrightarrow 00{:}20{:}37.868$ in the inhibitory neurons coming

NOTE Confidence: 0.94383830444445

 $00:20:37.868 \rightarrow 00:20:39.840$ out of that ganglionic evidence.

NOTE Confidence: 0.94383830444445

 $00:20:39.840 \rightarrow 00:20:42.840$ It stays on all the way into adulthood.

NOTE Confidence: 0.94383830444445

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

NOTE Confidence: 0.94383830444445

 $00:20:45.240 \longrightarrow 00:20:47.282$ role differential roles in these

NOTE Confidence: 0.94383830444445

 $00:20:47.282 \longrightarrow 00:20:49.466$ two different stem cells all the

NOTE Confidence: 0.94383830444445

 $00:20:49.466 \longrightarrow 00:20:51.640$ way into the mature neuron.

NOTE Confidence: 0.94383830444445

 $00:20:51.640 \longrightarrow 00:20:54.680$ So to study this what we did is

NOTE Confidence: 0.94383830444445

 $00:20:54.680 \longrightarrow 00:20:56.919$ we generated a mouse that had

NOTE Confidence: 0.94383830444445

 $00:20:56.920 \longrightarrow 00:20:59.237$ a that that was a Flox mouse.

NOTE Confidence: 0.94383830444445

 $00:20:59.240 \longrightarrow 00:21:01.160$ It has we inserted crease it

NOTE Confidence: 0.94383830444445

 $00{:}21{:}01{.}160 \dashrightarrow 00{:}21{:}03{.}398$ was on either side of Exxon two.

NOTE Confidence: 0.94383830444445

 $00:21:03.400 \rightarrow 00:21:05.787$ Remember Exxon two at the beginning of

NOTE Confidence: 0.94383830444445

 $00{:}21{:}05.787 \dashrightarrow 00{:}21{:}08.277$ the homeo domains when we remove Exxon 2.

NOTE Confidence: 0.94383830444445

 $00{:}21{:}08{.}280 \dashrightarrow 00{:}21{:}10{.}400$ It actually everything else is out of frame.

 $00:21:10.400 \longrightarrow 00:21:13.256$ You have no homeo domain and we

NOTE Confidence: 0.94383830444445

 $00:21:13.256 \longrightarrow 00:21:15.959$ believe this is a null mutation.

NOTE Confidence: 0.94383830444445

 $00{:}21{:}15{.}960 \dashrightarrow 00{:}21{:}18{.}096$ We could then cross this mouse

NOTE Confidence: 0.94383830444445

 $00:21:18.096 \rightarrow 00:21:20.645$ that we generated with a variety of

NOTE Confidence: 0.94383830444445

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

NOTE Confidence: 0.94383830444445

 $00{:}21{:}22.745 \dashrightarrow 00{:}21{:}25.461$ could remove a RX from just excitatory

NOTE Confidence: 0.94383830444445

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

NOTE Confidence: 0.94383830444445

 $00:21:29.800 \rightarrow 00:21:31.396$ Now to take one step back,

NOTE Confidence: 0.94383830444445

00:21:31.400 --> 00:21:32.102 a knockout,

NOTE Confidence: 0.94383830444445

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

NOTE Confidence: 0.94383830444445

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

NOTE Confidence: 0.94383830444445

 $00:21:37.400 \longrightarrow 00:21:38.942$ So we couldn't study any later

NOTE Confidence: 0.94383830444445

 $00:21:38.942 \longrightarrow 00:21:39.713$ effects with it.

NOTE Confidence: 0.94383830444445

 $00:21:39.720 \longrightarrow 00:21:41.862$ So we wanted to really hone down

NOTE Confidence: 0.94383830444445

 $00:21:41.862 \rightarrow 00:21:43.600$ on different regions of the brain.

NOTE Confidence: 0.94383830444445

 $00:21:43.600 \longrightarrow 00:21:44.360$ So that's what we did.
- NOTE Confidence: 0.94383830444445
- 00:21:44.360 00:21:47.438 So here we've crossed this mouse
- NOTE Confidence: 0.94383830444445
- $00:21:47.440 \longrightarrow 00:21:49.180$ with one that expresses creed
- NOTE Confidence: 0.94383830444445
- $00:21:49.180 \longrightarrow 00:21:50.920$ just in the ganglionic eminence.
- NOTE Confidence: 0.94383830444445
- $00:21:50.920 \longrightarrow 00:21:53.760$ And so ARX is normal in these
- NOTE Confidence: 0.94383830444445
- 00:21:53.760 --> 00:21:55.280 excitatory radially migrating cells,
- NOTE Confidence: 0.94383830444445
- $00:21:55.280 \longrightarrow 00:21:57.120$ but it's completely absent
- NOTE Confidence: 0.94383830444445
- $00:21:57.120 \longrightarrow 00:21:58.960$ from the ganglionic eminence.
- NOTE Confidence: 0.94383830444445
- $00:21:58.960 \longrightarrow 00:22:00.600$ And when we do that,
- NOTE Confidence: 0.94383830444445
- $00:22:00.600 \longrightarrow 00:22:02.040$ what we see and hopefully I'll
- NOTE Confidence: 0.94383830444445
- $00:22:02.040 \longrightarrow 00:22:03.000$ get this to work.
- NOTE Confidence: 0.9059009666666667
- $00:22:06.440 \longrightarrow 00:22:08.442$ There we go. So on your left
- NOTE Confidence: 0.9059009666666667
- $00{:}22{:}08{.}442 \dashrightarrow 00{:}22{:}10{.}360$ side is a normal brain.
- NOTE Confidence: 0.9059009666666667
- $00:22:10.360 \longrightarrow 00:22:12.980$ We've genetically labeled all the
- NOTE Confidence: 0.9059009666666667
- 00:22:12.980 --> 00:22:15.684 inhibitory neurons with a green dye
- NOTE Confidence: 0.9059009666666667
- $00{:}22{:}15.684 \dashrightarrow 00{:}22{:}17.798$ GFP and you can see them migrating
- NOTE Confidence: 0.9059009666666667

 $00:22:17.798 \rightarrow 00:22:19.602$ out of the ganglionic eminence

NOTE Confidence: 0.9059009666666667

 $00{:}22{:}19.602 \dashrightarrow 00{:}22{:}21.756$ up towards the cortex and then

NOTE Confidence: 0.9059009666666667

 $00:22:21.819 \rightarrow 00:22:23.955$ turning and going into the cortex.

NOTE Confidence: 0.9059009666666667

 $00:22:23.960 \longrightarrow 00:22:26.198$ Now what happens in the mutant

NOTE Confidence: 0.9059009666666667

 $00:22:26.200 \longrightarrow 00:22:27.016$ is that these cells,

NOTE Confidence: 0.9059009666666667

 $00{:}22{:}27.016 \dashrightarrow 00{:}22{:}28.240$ you don't see quite the connection,

NOTE Confidence: 0.9059009666666667

 $00:22:28.240 \longrightarrow 00:22:29.864$ but they're migrating out

NOTE Confidence: 0.9059009666666667

 $00:22:29.864 \rightarrow 00:22:31.520$ of the ganglionic eminence,

NOTE Confidence: 0.9059009666666667

 $00{:}22{:}31{.}520 \dashrightarrow 00{:}22{:}34{.}040$ they're going up into the cortex.

NOTE Confidence: 0.9059009666666667

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

NOTE Confidence: 0.9059009666666667

 $00:22:35.720 \longrightarrow 00:22:37.834$ but they don't turn out of their

NOTE Confidence: 0.9059009666666667

 $00:22:37.834 \rightarrow 00:22:40.119$ stream and go out into the cortex.

NOTE Confidence: 0.9059009666666667

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

NOTE Confidence: 0.9059009666666667

 $00:22:41.518 \rightarrow 00:22:42.680$ well you can see it,

NOTE Confidence: 0.9059009666666667

 $00{:}22{:}42.680 \dashrightarrow 00{:}22{:}44.175$ but there's cells migrating out

NOTE Confidence: 0.9059009666666667

 $00:22:44.175 \longrightarrow 00:22:46.382$ here in the marginal zone and those

- NOTE Confidence: 0.9059009666666667
- $00:22:46.382 \rightarrow 00:22:48.626$ are completely absent from the ARX.
- NOTE Confidence: 0.9059009666666667
- $00:22:48.626 \longrightarrow 00:22:50.736$ So it's completely eliminated one
- NOTE Confidence: 0.9059009666666667
- $00:22:50.736 \longrightarrow 00:22:52.923$ stream of these inhibitory neurons
- NOTE Confidence: 0.9059009666666667
- $00{:}22{:}52{.}923 \dashrightarrow 00{:}22{:}55{.}877$ and it's there's a defect in the
- NOTE Confidence: 0.9059009666666667
- $00{:}22{:}55{.}953 \dashrightarrow 00{:}22{:}58{.}248$ migration of that other stream.
- NOTE Confidence: 0.9059009666666667
- $00:22:58.250 \rightarrow 00:22:59.810$ Now when we study these mice,
- NOTE Confidence: 0.9059009666666667
- $00:22:59.810 \longrightarrow 00:23:01.142$ I can tell you the brain
- NOTE Confidence: 0.9059009666666667
- $00:23:01.142 \longrightarrow 00:23:01.808$ is structurally normal.
- NOTE Confidence: 0.9059009666666667
- $00:23:01.810 \longrightarrow 00:23:02.770$ This has all been published,
- NOTE Confidence: 0.9059009666666667
- 00:23:02.770 --> 00:23:04.450 so I'm not going to go through details.
- NOTE Confidence: 0.9059009666666667
- $00:23:04.450 \longrightarrow 00:23:05.970$ The brain is structurally normal.
- NOTE Confidence: 0.9059009666666667
- $00{:}23{:}05{.}970 \dashrightarrow 00{:}23{:}08{.}410$ The corpus callosum is intact.
- NOTE Confidence: 0.9059009666666667
- $00:23:08.410 \longrightarrow 00:23:11.090$ The cell layers are intact.
- NOTE Confidence: 0.9059009666666667
- $00:23:11.090 \rightarrow 00:23:13.337$ Every single one of these mice that
- NOTE Confidence: 0.9059009666666667
- $00:23:13.337 \rightarrow 00:23:15.262$ we've tested has epilepsy from the
- NOTE Confidence: 0.9059009666666667

 $00:23:15.262 \longrightarrow 00:23:17.590$ very first time we can look at it.

NOTE Confidence: 0.9059009666666667

 $00{:}23{:}17{.}590 \dashrightarrow 00{:}23{:}20{.}026$ So they develop different types of epilepsy.

NOTE Confidence: 0.9059009666666667

 $00{:}23{:}20{.}030 \dashrightarrow 00{:}23{:}22{.}284$ We see these spikes and slow wave

NOTE Confidence: 0.9059009666666667

 $00:23:22.284 \rightarrow 00:23:24.004$ with an electrical decrement like

NOTE Confidence: 0.9059009666666667

 $00{:}23{:}24.004 \dashrightarrow 00{:}23{:}26.426$ here that's what you see in children

NOTE Confidence: 0.9059009666666667

 $00:23:26.426 \rightarrow 00:23:28.390$ with infantile spasm syndrome,

NOTE Confidence: 0.9059009666666667

 $00:23:28.390 \longrightarrow 00:23:30.946$ exactly like what you see with

NOTE Confidence: 0.9059009666666667

 $00{:}23{:}30{.}946 \dashrightarrow 00{:}23{:}32{.}224$ the ARX mutations.

NOTE Confidence: 0.9059009666666667

 $00{:}23{:}32{.}230 \dashrightarrow 00{:}23{:}34{.}105$ These are these Jacksonian type

NOTE Confidence: 0.9059009666666667

 $00{:}23{:}34{.}105 \dashrightarrow 00{:}23{:}35{.}980$ seizures which start and then

NOTE Confidence: 0.9059009666666667

 $00{:}23{:}36{.}043 \dashrightarrow 00{:}23{:}37{.}947$ propagate throughout the brain.

NOTE Confidence: 0.9059009666666667

 $00:23:37.950 \longrightarrow 00:23:40.771$ So we see an evolution and different

NOTE Confidence: 0.9059009666666667

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

NOTE Confidence: 0.9059009666666667

 $00{:}23{:}43.030 \dashrightarrow 00{:}23{:}45.424$ the earliest time we can record it.

NOTE Confidence: 0.9059009666666667

 $00{:}23{:}45{.}430 \dashrightarrow 00{:}23{:}47{.}998$ So these mice all have seizures.

NOTE Confidence: 0.9059009666666667

 $00:23:48.000 \longrightarrow 00:23:51.280$ And the brains, as I said,

- NOTE Confidence: 0.9059009666666667
- $00:23:51.280 \longrightarrow 00:23:53.560$ are completely normal.
- NOTE Confidence: 0.9059009666666667
- 00:23:53.560 --> 00:23:57.360 Now in contrast, if we remove a RX,
- NOTE Confidence: 0.9059009666666667
- $00:23:57.360 \rightarrow 00:23:59.760$ instead of from the ganglionic Eminence,
- NOTE Confidence: 0.9059009666666667
- $00{:}23{:}59.760 \dashrightarrow 00{:}24{:}02.370$ we remove it from the excited where
- NOTE Confidence: 0.9059009666666667
- $00:24:02.370 \longrightarrow 00:24:04.595$ the excitatory neurons are being
- NOTE Confidence: 0.9059009666666667
- 00:24:04.595 --> 00:24:07.320 derived using a different Cree driver,
- NOTE Confidence: 0.9059009666666667
- $00:24:07.320 \longrightarrow 00:24:09.540$ what we see is something
- NOTE Confidence: 0.9059009666666667
- $00:24:09.540 \longrightarrow 00:24:10.428$ completely different.
- NOTE Confidence: 0.9059009666666667
- $00:24:10.430 \longrightarrow 00:24:12.182$ Now what you see is that
- NOTE Confidence: 0.9059009666666667
- $00:24:12.182 \longrightarrow 00:24:13.830$ the the brains are small.
- NOTE Confidence: 0.9059009666666667
- 00:24:13.830 --> 00:24:15.954 Remember I told you the brains
- NOTE Confidence: 0.9059009666666667
- $00{:}24{:}15{.}954 \dashrightarrow 00{:}24{:}17{.}830$ are structurally normal with the
- NOTE Confidence: 0.9059009666666667
- $00{:}24{:}17.830 \dashrightarrow 00{:}24{:}19.830$ removal from the inhibitory neurons.
- NOTE Confidence: 0.9059009666666667
- $00:24:19.830 \longrightarrow 00:24:21.390$ The cortex is very thin,
- NOTE Confidence: 0.9059009666666667
- $00{:}24{:}21{.}390 \dashrightarrow 00{:}24{:}23{.}202$ it's actually dislaminated and
- NOTE Confidence: 0.9059009666666667

 $00:24:23.202 \rightarrow 00:24:25.467$ you have no corpus callosum.

NOTE Confidence: 0.9059009666666667

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

NOTE Confidence: 0.9059009666666667

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

NOTE Confidence: 0.9059009666666667

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

NOTE Confidence: 0.9059009666666667

 $00:24:30.990 \longrightarrow 00:24:33.792$ So by removing it from the

NOTE Confidence: 0.9059009666666667

00:24:33.792 --> 00:24:35.660 excitatory projection neurons you

NOTE Confidence: 0.9059009666666667

 $00:24:35.737 \longrightarrow 00:24:38.147$ get all the structural defects.

NOTE Confidence: 0.9059009666666667

00:24:38.150 - 00:24:40.229 That you get none of the epilepsy.

NOTE Confidence: 0.9059009666666667

 $00{:}24{:}40{.}230 \dashrightarrow 00{:}24{:}41{.}586$ We've looked at hundreds of mice.

NOTE Confidence: 0.9059009666666667

 $00{:}24{:}41{.}590 \dashrightarrow 00{:}24{:}44{.}350$ We've never seen a seizure.

NOTE Confidence: 0.9059009666666667

 $00:24:44.350 \longrightarrow 00:24:46.460$ So now we're starting to

NOTE Confidence: 0.9059009666666667

 $00{:}24{:}46{.}460 \dashrightarrow 00{:}24{:}48{.}483$ distinguish where does the kind

NOTE Confidence: 0.9059009666666667

 $00{:}24{:}48{.}483 \dashrightarrow 00{:}24{:}50{.}148$ of cognitive behavioral and where

NOTE Confidence: 0.9059009666666667

 $00{:}24{:}50{.}148 \dashrightarrow 00{:}24{:}52{.}460$ do some of the other neurologic

NOTE Confidence: 0.9059009666666667

 $00:24:52.460 \rightarrow 00:24:54.750$ phenotypes where they derive from,

NOTE Confidence: 0.9059009666666667

 $00:24:54.750 \longrightarrow 00:24:56.425$ from a cell migration standpoint

- NOTE Confidence: 0.9059009666666667
- $00:24:56.425 \rightarrow 00:24:58.100$ and and this just shows.
- NOTE Confidence: 0.9059009666666667
- $00{:}24{:}58{.}100 \dashrightarrow 00{:}25{:}00{.}020$ The disruption of the cortical lamination,
- NOTE Confidence: 0.9059009666666667
- $00:25:00.020 \rightarrow 00:25:03.188$ we can look at at specific genes that
- NOTE Confidence: 0.9059009666666667
- $00{:}25{:}03.188 \dashrightarrow 00{:}25{:}05.561$ are expressed in specific laminate
- NOTE Confidence: 0.9059009666666667
- $00{:}25{:}05{.}561 \dashrightarrow 00{:}25{:}07{.}553$ and show defects predominantly
- NOTE Confidence: 0.9059009666666667
- 00:25:07.553 00:25:10.060 in the upper layer cells.
- NOTE Confidence: 0.9059009666666667
- $00:25:10.060 \rightarrow 00:25:12.300$ And those upper layer cells in the
- NOTE Confidence: 0.9553487
- $00:25:12.300 \rightarrow 00:25:14.500$ mouse come from those intermediate
- NOTE Confidence: 0.9553487
- $00{:}25{:}14.500 \dashrightarrow 00{:}25{:}16.700$ progenitor cells that I mentioned.
- NOTE Confidence: 0.9553487
- $00{:}25{:}16.700 \dashrightarrow 00{:}25{:}18.940$ And so we looked at those intermediate
- NOTE Confidence: 0.9553487
- $00:25:18.940 \longrightarrow 00:25:20.660$ progenitor cells and what we found
- NOTE Confidence: 0.9553487
- $00{:}25{:}20.660 \dashrightarrow 00{:}25{:}23.516$ 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
- $00{:}25{:}29{.}720 \dashrightarrow 00{:}25{:}31{.}484$ and that's a gene that's important for
- NOTE Confidence: 0.9553487

 $00{:}25{:}31{.}484 \dashrightarrow 00{:}25{:}33{.}478$ cells being able to reenter the cell cycle.

NOTE Confidence: 0.9553487

 $00{:}25{:}33{.}480 \dashrightarrow 00{:}25{:}35{.}358$ So what's happening is these cells,

NOTE Confidence: 0.9553487

 $00:25:35.360 \rightarrow 00:25:38.940$ because they no longer express the CDKN 1C,

NOTE Confidence: 0.9553487

 $00:25:38.940 \rightarrow 00:25:42.000$ are exiting the cell cycle prematurely.

NOTE Confidence: 0.9553487

 $00{:}25{:}42.000 \dashrightarrow 00{:}25{:}44.525$ Therefore you're not getting the

NOTE Confidence: 0.9553487

 $00{:}25{:}44.525 \dashrightarrow 00{:}25{:}47.640$ correct number of of rounds of mitosis

NOTE Confidence: 0.9553487

 $00:25:47.640 \longrightarrow 00:25:49.240$ in the intermediate progenitor

NOTE Confidence: 0.9553487

 $00:25:49.240 \longrightarrow 00:25:51.972$ cell and you've got a defect in

NOTE Confidence: 0.9553487

 $00{:}25{:}51{.}972 \dashrightarrow 00{:}25{:}53{.}837$ those mostly upper layer neurons.

NOTE Confidence: 0.934383218333333

 $00{:}25{:}55{.}900 \dashrightarrow 00{:}25{:}59{.}284$ We can actually test that by going in

NOTE Confidence: 0.934383218333333

 $00{:}25{:}59{.}284 \dashrightarrow 00{:}26{:}02{.}740$ and we built a a system to actually

NOTE Confidence: 0.934383218333333

 $00{:}26{:}02.740 \dashrightarrow 00{:}26{:}04.580$ repress actually what happened.

NOTE Confidence: 0.934383218333333

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

NOTE Confidence: 0.934383218333333

 $00:26:05.840 \rightarrow 00:26:07.988$ There's over expression of the CDKN 1C.

NOTE Confidence: 0.934383218333333

 $00{:}26{:}07{.}988 \dashrightarrow 00{:}26{:}09{.}976$ The ARX is a repressor of that.

NOTE Confidence: 0.934383218333333

 $00{:}26{:}09{.}980 \dashrightarrow 00{:}26{:}12{.}689$ We then knocked it down and we can see

- NOTE Confidence: 0.934383218333333
- $00:26:12.689 \rightarrow 00:26:15.603$ the return of the proliferation and we
- NOTE Confidence: 0.934383218333333
- $00:26:15.603 \rightarrow 00:26:18.301$ actually can rescue that phenotype of
- NOTE Confidence: 0.934383218333333
- $00:26:18.301 \rightarrow 00:26:21.097$ loss of the mostly superficial neurons.
- NOTE Confidence: 0.934383218333333
- $00:26:21.100 \longrightarrow 00:26:23.746$ So this showed that that was one of the
- NOTE Confidence: 0.934383218333333
- $00:26:23.746 \rightarrow 00:26:25.618$ mechanisms by which ARX was functioning.
- NOTE Confidence: 0.931867333333333
- $00:26:28.470 \longrightarrow 00:26:31.068$ 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
- $00:26:32.840 \longrightarrow 00:26:34.890$ to this set of two kids.
- NOTE Confidence: 0.931867333333333
- $00:26:34.890 \longrightarrow 00:26:37.692$ Now at the top is a child
- NOTE Confidence: 0.931867333333333
- $00:26:37.692 \longrightarrow 00:26:40.227$ 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
- $00:26:43.052 \rightarrow 00:26:45.344$ epilepsy starting at about six months
- NOTE Confidence: 0.931867333333333
- $00{:}26{:}45{.}350 \dashrightarrow 00{:}26{:}47{.}374$ in severe intellectual disabilities,
- NOTE Confidence: 0.931867333333333
- $00{:}26{:}47{.}374 \dashrightarrow 00{:}26{:}50{.}410$ never was able to feed himself.
- NOTE Confidence: 0.931867333333333
- $00:26:50.410 \longrightarrow 00:26:52.545$ 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: 0.931867333333333

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

NOTE Confidence: 0.931867333333333

00:26:55.970 --> 00:26:57.048 brain lizencephaly.

NOTE Confidence: 0.931867333333333

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

NOTE Confidence: 0.931867333333333

 $00{:}26{:}59{.}743 \dashrightarrow 00{:}27{:}01{.}850$ in this posterior part.

NOTE Confidence: 0.931867333333333

 $00:27:01.850 \longrightarrow 00:27:04.886$ There's no suicide here at all.

NOTE Confidence: 0.931867333333333

 $00:27:04.890 \longrightarrow 00:27:06.770$ Here you can see posteriorly.

NOTE Confidence: 0.931867333333333

 $00{:}27{:}06{.}770 \dashrightarrow 00{:}27{:}09{.}962$ Now the child at the bottom also has

NOTE Confidence: 0.931867333333333

 $00{:}27{:}09{.}962 \dashrightarrow 00{:}27{:}12{.}971$ an ARX mutation, also had epilepsy.

NOTE Confidence: 0.931867333333333

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

NOTE Confidence: 0.9318673333333333

 $00{:}27{:}16.839 \dashrightarrow 00{:}27{:}19.544$ and had severe intellectual disability.

NOTE Confidence: 0.931867333333333

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

NOTE Confidence: 0.931867333333333

 $00:27:23.910 \longrightarrow 00:27:27.213$ The brain of the child at the top had NOTE Confidence: 0.931867333333333

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

NOTE Confidence: 0.931867333333333

 $00:27:30.938 \longrightarrow 00:27:33.885$ The child at the bottom had an

NOTE Confidence: 0.931867333333333

 $00{:}27{:}33.885 \dashrightarrow 00{:}27{:}36.469$ alanine tract expansion mutation.

 $00:27:36.470 \rightarrow 00:27:39.470$ Now if we think about what I just told you,

NOTE Confidence: 0.931867333333333

 $00:27:39.470 \longrightarrow 00:27:41.110$ the brain is structurally normal,

NOTE Confidence: 0.931867333333333

00:27:41.110 - 00:27:44.142 but you have the seizures if you have

NOTE Confidence: 0.931867333333333

 $00:27:44.142 \rightarrow 00:27:47.208$ a defect in your inhibitory neurons.

NOTE Confidence: 0.931867333333333

 $00:27:47.210 \longrightarrow 00:27:48.218$ But it's only when you have

NOTE Confidence: 0.931867333333333

 $00:27:48.218 \longrightarrow 00:27:49.330$ a defect in the migration,

NOTE Confidence: 0.931867333333333

 $00:27:49.330 \rightarrow 00:27:52.048$ the movement of those excitatory neurons

NOTE Confidence: 0.931867333333333

 $00:27:52.050 \longrightarrow 00:27:54.888$ that you have the structural defects.

NOTE Confidence: 0.931867333333333

 $00{:}27{:}54.890 \dashrightarrow 00{:}27{:}56.546$ So we predicted that that's what

NOTE Confidence: 0.931867333333333

 $00:27:56.546 \longrightarrow 00:27:58.568$ we would see if we tested this.

NOTE Confidence: 0.931867333333333

 $00:27:58.570 \rightarrow 00:28:02.170$ So that's what we did experimentally.

NOTE Confidence: 0.931867333333333

 $00:28:02.170 \longrightarrow 00:28:03.650$ So to do these experiments,

NOTE Confidence: 0.931867333333333

 $00:28:03.650 \rightarrow 00:28:05.369$ we went in and and you can do something

NOTE Confidence: 0.931867333333333

 $00{:}28{:}05{.}369 \dashrightarrow 00{:}28{:}06{.}608$ called in utero electropration.

NOTE Confidence: 0.931867333333333

 $00{:}28{:}06{.}610 \dashrightarrow 00{:}28{:}09{.}290$ This is where you can take a mouse,

00:28:09.290 --> 00:28:10.658 a gravid mom,

NOTE Confidence: 0.931867333333333

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

NOTE Confidence: 0.931867333333333

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

NOTE Confidence: 0.931867333333333

 $00:28:15.664 \rightarrow 00:28:17.884$ an expression construct into the

NOTE Confidence: 0.931867333333333

 $00{:}28{:}17{.}884 \dashrightarrow 00{:}28{:}20{.}264$ ventricle of the into the pup while

NOTE Confidence: 0.931867333333333

 $00:28:20.264 \longrightarrow 00:28:22.238$ it's in the uterus and you put

NOTE Confidence: 0.931867333333333

 $00:28:22.238 \rightarrow 00:28:23.978$ these electrodes on either side,

NOTE Confidence: 0.931867333333333

 $00{:}28{:}23.980 \dashrightarrow 00{:}28{:}25.200$ you electroplate it just like

NOTE Confidence: 0.931867333333333

 $00{:}28{:}25{.}200 \dashrightarrow 00{:}28{:}26{.}420$ you would in a gel.

NOTE Confidence: 0.931867333333333

 $00{:}28{:}26{.}420 \dashrightarrow 00{:}28{:}29{.}276$ The DNA goes into the brain and then

NOTE Confidence: 0.931867333333333

 $00:28:29.276 \longrightarrow 00:28:32.275$ you can actually return the grab the

NOTE Confidence: 0.931867333333333

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

NOTE Confidence: 0.931867333333333

00:28:34.060 - 00:28:36.334 and those mice can go on and even be

NOTE Confidence: 0.931867333333333

 $00{:}28{:}36{.}334 \dashrightarrow 00{:}28{:}38{.}578$ delivered so we can study them later

NOTE Confidence: 0.931867333333333

 $00:28:38.580 \rightarrow 00:28:41.650$ and what you see is if you do that normally.

NOTE Confidence: 0.931867333333333

 $00:28:41.650 \dashrightarrow 00:28:43.526$ The cells migrate out to the cortex.

- NOTE Confidence: 0.931867333333333
- $00:28:43.530 \longrightarrow 00:28:46.078$ So this is just with the GFP
- NOTE Confidence: 0.931867333333333
- 00:28:46.078 --> 00:28:48.248 electroprated into our ARX Flox mice,
- NOTE Confidence: 0.931867333333333
- $00{:}28{:}48{.}250 \dashrightarrow 00{:}28{:}49{.}278$ no Cree.
- NOTE Confidence: 0.931867333333333
- $00:28:49.278 \longrightarrow 00:28:51.848$ So they're just wild type.
- NOTE Confidence: 0.931867333333333
- 00:28:51.850 --> 00:28:54.025 If we introduce a brain
- NOTE Confidence: 0.931867333333333
- $00:28:54.025 \rightarrow 00:28:56.674$ four or this how 3F4 Cree.
- NOTE Confidence: 0.931867333333333
- $00:28:56.674 \rightarrow 00:29:00.250$ What you see when you electroprate in GFP,
- NOTE Confidence: 0.931867333333333
- $00:29:00.250 \rightarrow 00:29:02.567$ now they've lost all of their ARX.
- NOTE Confidence: 0.931867333333333
- $00:29:02.570 \longrightarrow 00:29:05.727$ You see that these cells don't migrate.
- NOTE Confidence: 0.931867333333333
- $00:29:05.730 \rightarrow 00:29:08.484$ If we rescue this with a wild type ARX,
- NOTE Confidence: 0.931867333333333
- $00{:}29{:}08{.}490 \dashrightarrow 00{:}29{:}10{.}488$ you see the cells migrate out to the surface,
- NOTE Confidence: 0.931867333333333
- $00:29:10.490 \longrightarrow 00:29:11.930$ just not very nicely.
- NOTE Confidence: 0.931867333333333
- $00:29:11.930 \longrightarrow 00:29:14.090$ You have a very nice rescue.
- NOTE Confidence: 0.931867333333333
- 00:29:14.090 --> 00:29:16.570 But if you do that with the sorry,
- NOTE Confidence: 0.931867333333333
- $00{:}29{:}16{.}570 \dashrightarrow 00{:}29{:}18{.}723$ and if you do that with the ARX
- NOTE Confidence: 0.931867333333333

 $00:29:18.723 \rightarrow 00:29:21.088$ that has that expansion mutation,

NOTE Confidence: 0.931867333333333

 $00{:}29{:}21.090 \dashrightarrow 00{:}29{:}23.286$ you also rescue that radial migration.

NOTE Confidence: 0.931867333333333

 $00{:}29{:}23{.}290 \dashrightarrow 00{:}29{:}25{.}649$ These cells migrate out to the surface.

NOTE Confidence: 0.931867333333333

 $00:29:25.650 \longrightarrow 00:29:27.990$ So the expansion mutation doesn't seem

NOTE Confidence: 0.931867333333333

 $00:29:27.990 \longrightarrow 00:29:30.090$ to affect these excitatory neurons,

NOTE Confidence: 0.931867333333333

 $00:29:30.090 \rightarrow 00:29:31.805$ at least their ability to migrate out.

NOTE Confidence: 0.95175457

 $00:29:35.660 \rightarrow 00:29:38.138$ Now contrast that to the inhibitory neurons.

NOTE Confidence: 0.95175457

 $00:29:38.140 \rightarrow 00:29:40.534$ So now what we've done is when you put

NOTE Confidence: 0.95175457

 $00{:}29{:}40{.}534 \dashrightarrow 00{:}29{:}42{.}724$ it in the wild type, the cells migrate

NOTE Confidence: 0.95175457

 $00:29:42.724 \rightarrow 00:29:44.460$ out very nicely up into the cortex.

NOTE Confidence: 0.95175457

 $00:29:44.460 \longrightarrow 00:29:46.480$ So now we've just electroplate

NOTE Confidence: 0.95175457

 $00:29:46.480 \longrightarrow 00:29:48.096$ into the ganglionic eminence.

NOTE Confidence: 0.95175457

 $00{:}29{:}48.100 \dashrightarrow 00{:}29{:}50.494$ The cells migrate up when you put it in,

NOTE Confidence: 0.95175457

 $00:29:50.500 \rightarrow 00:29:53.056$ when you remove a RX from the whole brain,

NOTE Confidence: 0.95175457

 $00{:}29{:}53.060 \dashrightarrow 00{:}29{:}54.190$ you see that these cells

NOTE Confidence: 0.95175457

 $00:29:54.190 \rightarrow 00:29:55.094$ no longer migrate up.

- NOTE Confidence: 0.95175457
- 00:29:55.100 > 00:29:57.396 They kind of get stuck down here

 $00:29:57.396 \longrightarrow 00:29:59.620$ in what will become striatum.

NOTE Confidence: 0.95175457

 $00:29:59.620 \rightarrow 00:30:02.300$ If we rescue with the wild type ARX,

NOTE Confidence: 0.95175457

 $00{:}30{:}02{.}300 \dashrightarrow 00{:}30{:}04{.}246$ you can see that again these cells

NOTE Confidence: 0.95175457

 $00:30:04.246 \rightarrow 00:30:05.800$ are migrating up very nicely.

NOTE Confidence: 0.95175457

 $00:30:05.800 \longrightarrow 00:30:07.560$ Yeah, you can see that.

NOTE Confidence: 0.95175457

 $00{:}30{:}07{.}560 \dashrightarrow 00{:}30{:}09{.}310$ But if we do that with the

NOTE Confidence: 0.95175457

 $00:30:09.310 \longrightarrow 00:30:10.560$ alanine tract expansion mutation,

NOTE Confidence: 0.95175457

 $00:30:10.560 \longrightarrow 00:30:12.800$ they don't.

NOTE Confidence: 0.95175457

 $00:30:12.800 \longrightarrow 00:30:16.106$ So the alanine tract expansion seems

NOTE Confidence: 0.95175457

 $00:30:16.106 \dashrightarrow 00:30:18.740$ to be differentially affecting

NOTE Confidence: 0.95175457

 $00{:}30{:}18.740 \dashrightarrow 00{:}30{:}22.625$ the inhibitory neurons and a whole

NOTE Confidence: 0.95175457

 $00:30:22.625 \dashrightarrow 00:30:24.515$ series of experiments that we did,

NOTE Confidence: 0.95175457

 $00{:}30{:}24{.}520 \dashrightarrow 00{:}30{:}27{.}810$ 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

 $00:30:35.570 \longrightarrow 00:30:37.610$ So in the inhibitory neurons,

NOTE Confidence: 0.95175457

 $00:30:37.610 \longrightarrow 00:30:39.165$ 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

 $00:30:41.730 \longrightarrow 00:30:43.930$ isolated to 1 transcription factor,

NOTE Confidence: 0.95175457

 $00:30:43.930 \rightarrow 00:30:46.030$ it's a transcriptional complex usually

NOTE Confidence: 0.95175457

 $00:30:46.030 \longrightarrow 00:30:48.810$ with 40 to 60 different proteins.

NOTE Confidence: 0.95175457

 $00{:}30{:}48.810 \dashrightarrow 00{:}30{:}51.230$ And so this complex usually

NOTE Confidence: 0.95175457

 $00{:}30{:}51{.}230 \dashrightarrow 00{:}30{:}53{.}166$ has stabilizers and cofactors.

NOTE Confidence: 0.95175457

 $00{:}30{:}53.170 \dashrightarrow 00{:}30{:}56.176$ And what happens in the we showed

NOTE Confidence: 0.95175457

 $00:30:56.176 \rightarrow 00:30:57.754$ 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

 $00:31:01.905 \longrightarrow 00:31:04.665$ which is a gaucho like transcriptional

NOTE Confidence: 0.95175457

 $00{:}31{:}04.665 \dashrightarrow 00{:}31{:}06.575$ repressor involved in repressing

NOTE Confidence: 0.95175457

 $00:31:06.575 \dashrightarrow 00:31:10.112$ things like Ed F3 and also that CDKN

 $00:31:10.112 \rightarrow 00:31:13.808$ 1C that I mentioned no longer get repressed.

NOTE Confidence: 0.95175457

 $00:31:13.810 \rightarrow 00:31:16.302$ They continue to be overexpressed and that

NOTE Confidence: 0.95175457

 $00:31:16.302 \rightarrow 00:31:19.010$ leads to defects in these inhibitory norms.

NOTE Confidence: 0.95175457

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

NOTE Confidence: 0.95175457

 $00:31:19.661 \dashrightarrow 00:31:21.614$ the transcriptional complex

NOTE Confidence: 0.95175457

 $00:31:21.614 \rightarrow 00:31:23.567$ is structurally different.

NOTE Confidence: 0.95175457

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

NOTE Confidence: 0.95175457

 $00{:}31{:}25{.}235 \dashrightarrow 00{:}31{:}27{.}339$ that even with that polyne alanine

NOTE Confidence: 0.95175457

 $00{:}31{:}27{.}339 \dashrightarrow 00{:}31{:}29{.}583$ tract expansion that leads to a

NOTE Confidence: 0.95175457

 $00:31:29.583 \rightarrow 00:31:31.529$ 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

 $00{:}31{:}37{.}285 \dashrightarrow 00{:}31{:}39{.}680$ 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

 $00{:}31{:}42.740 \dashrightarrow 00{:}31{:}44.850$ the excitatory neuron migration.

 $00:31:44.850 \longrightarrow 00:31:47.433$ 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

 $00{:}31{:}52.890 \dashrightarrow 00{:}31{:}54.810$ in different progenitor cells

NOTE Confidence: 0.95175457

 $00:31:54.810 \rightarrow 00:31:56.730$ leading to different phenotypes.

NOTE Confidence: 0.95175457

 $00{:}31{:}56{.}730 \dashrightarrow 00{:}31{:}59{.}778$ Whereas in in if you remove a RX

NOTE Confidence: 0.95175457

 $00{:}31{:}59{.}778 \dashrightarrow 00{:}32{:}02{.}410$ it'll affect both of them together

NOTE Confidence: 0.95175457

 $00{:}32{:}02{.}410 \dashrightarrow 00{:}32{:}04.695$ and that's what happens with

NOTE Confidence: 0.95175457

 $00{:}32{:}04.695 \dashrightarrow 00{:}32{:}06.523$ the Liz encephaly phenotype.

NOTE Confidence: 0.95175457

 $00{:}32{:}06{.}530 \dashrightarrow 00{:}32{:}10{.}592$ Now we went on to take a non

NOTE Confidence: 0.95175457

 $00{:}32{:}10.592 \dashrightarrow 00{:}32{:}13.147$ unbiased proteomics approach to say.

NOTE Confidence: 0.95175457

 $00:32:13.150 \rightarrow 00:32:14.190$ Wow, this is really interesting.

NOTE Confidence: 0.95175457

 $00:32:14.190 \longrightarrow 00:32:15.370$ What are all the proteins

NOTE Confidence: 0.95175457

 $00{:}32{:}15{.}370 \dashrightarrow 00{:}32{:}16{.}550$ that interact with a RX?

NOTE Confidence: 0.95175457

 $00{:}32{:}16.550 \dashrightarrow 00{:}32{:}19.287$ Because we want to understand that whole

 $00:32:19.287 \rightarrow 00:32:21.108$ transcriptional complex and we actually

NOTE Confidence: 0.95175457

 $00{:}32{:}21.108 \dashrightarrow 00{:}32{:}23.184$ 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

 $00{:}32{:}25.845 \dashrightarrow 00{:}32{:}27.801$ 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

 $00{:}32{:}29{.}590 \dashrightarrow 00{:}32{:}30{.}654$ and I'm going to come back to

NOTE Confidence: 0.95175457

 $00:32:30.654 \longrightarrow 00:32:31.430$ that in a minute.

NOTE Confidence: 0.95175457

 $00:32:31.430 \longrightarrow 00:32:33.201$ What we did find is a number

NOTE Confidence: 0.95175457

 $00:32:33.201 \longrightarrow 00:32:34.868$ of things that are involved in

NOTE Confidence: 0.95175457

 $00:32:34.868 \longrightarrow 00:32:36.434$ the when signaling pathway,

NOTE Confidence: 0.95175457

 $00{:}32{:}36{.}434 \dashrightarrow 00{:}32{:}38{.}574$ which is important for proliferation

NOTE Confidence: 0.95175457

 $00{:}32{:}38{.}574 \dashrightarrow 00{:}32{:}40{.}492$ in those cortical ventricular cells.

NOTE Confidence: 0.95175457

 $00{:}32{:}40{.}492 \dashrightarrow 00{:}32{:}42{.}970$ So I'm not going to that's that's

NOTE Confidence: 0.95175457

 $00{:}32{:}43.034 \dashrightarrow 00{:}32{:}44.078$ work we published.

NOTE Confidence: 0.95175457

 $00{:}32{:}44.080 \dashrightarrow 00{:}32{:}45.800$ I'm not going to talk about it today.

 $00{:}32{:}45{.}800 \dashrightarrow 00{:}32{:}49{.}363$ But we also found that it affected

NOTE Confidence: 0.95175457

 $00:32:49.363 \rightarrow 00:32:52.078$ dorsal ventral patterning in the brain.

NOTE Confidence: 0.935608953846154

 $00{:}32{:}52{.}080 \dashrightarrow 00{:}32{:}55{.}491$ So if you take the brain and this is

NOTE Confidence: 0.935608953846154

 $00:32:55.491 \rightarrow 00:32:57.651$ expression of Olig 2, some work we

NOTE Confidence: 0.935608953846154

 $00:32:57.651 \dashrightarrow 00:32:59.818$ 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

 $00:33:03.314 \rightarrow 00:33:06.658$ RX is normally sorry where all Olig 2.

NOTE Confidence: 0.935608953846154

 $00:33:06.660 \rightarrow 00:33:08.796$ Stops being expressed, and you can

NOTE Confidence: 0.935608953846154

 $00:33:08.796 \dashrightarrow 00:33:11.236$ see that here in the coronal plane.

NOTE Confidence: 0.935608953846154

 $00:33:11.236 \dashrightarrow 00:33:14.896$ And if you look at it in the sagittal plane,

NOTE Confidence: 0.935608953846154

 $00{:}33{:}14.896 \dashrightarrow 00{:}33{:}18.528$ you can see that it stops at the top of

NOTE Confidence: 0.935608953846154

 $00{:}33{:}18.528 \dashrightarrow 00{:}33{:}21.336$ that gang, that lateral ganglionic eminence.

NOTE Confidence: 0.935608953846154

 $00:33:21.340 \longrightarrow 00:33:23.500$ 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

 $00:33:24.856 \longrightarrow 00:33:27.260$ You can see that this olive two,

NOTE Confidence: 0.935608953846154

 $00:33:27.260 \longrightarrow 00:33:29.160$ 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
- $00:33:33.168 \longrightarrow 00:33:35.276$ across the dorsal cortex.
- NOTE Confidence: 0.935608953846154
- $00:33:35.280 \rightarrow 00:33:37.872$ And you can see it going up beyond where
- NOTE Confidence: 0.935608953846154
- $00:33:37.872 \rightarrow 00:33:41.216$ we would normally see it in the wild type.
- NOTE Confidence: 0.935608953846154
- $00:33:41.216 \rightarrow 00:33:43.580$ 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
- $00:33:45.640 \rightarrow 00:33:48.797$ it was affecting patterning of the brain.
- NOTE Confidence: 0.935608953846154
- $00:33:48.800 \rightarrow 00:33:51.880$ So what's important about that?
- NOTE Confidence: 0.935608953846154
- $00:33:51.880 \rightarrow 00:33:53.736$ Oh, so we went on and showed that
- NOTE Confidence: 0.935608953846154
- $00:33:53.736 \rightarrow 00:33:55.478$ it's not just the wind 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
- $00{:}33{:}59{.}081 \dashrightarrow 00{:}34{:}01{.}419$ were able to separate out all these
- NOTE Confidence: 0.935608953846154
- $00{:}34{:}01{.}419 \dashrightarrow 00{:}34{:}03{.}689$ pathways and how that was affecting
- NOTE Confidence: 0.935608953846154

 $00:34:03.689 \dashrightarrow 00:34:06.089$ all of two and downstream components.

NOTE Confidence: 0.935608953846154

00:34:06.090 --> 00:34:06.316 Again,

NOTE Confidence: 0.935608953846154

 $00:34:06.316 \longrightarrow 00:34:08.124$ these are not things I'm going to talk

NOTE Confidence: 0.935608953846154

 $00:34:08.124 \rightarrow 00:34:09.730$ 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

 $00{:}34{:}11{.}146 \dashrightarrow 00{:}34{:}13{.}506$ the reason we became interested

NOTE Confidence: 0.935608953846154

 $00:34:13.506 \longrightarrow 00:34:16.448$ in this patterning is because

NOTE Confidence: 0.935608953846154

 $00:34:16.450 \longrightarrow 00:34:19.467$ these mice as I've alluded to have

NOTE Confidence: 0.935608953846154

 $00{:}34{:}19{.}467 \dashrightarrow 00{:}34{:}21{.}452$ behavioral defects and we wanted

NOTE Confidence: 0.935608953846154

 $00{:}34{:}21{.}452 \dashrightarrow 00{:}34{:}23{.}322$ to understand what's the biologic

NOTE Confidence: 0.935608953846154

 $00{:}34{:}23{.}322 \dashrightarrow 00{:}34{:}25{.}820$ basis of these behavioral defects.

NOTE Confidence: 0.935608953846154

 $00:34:25.820 \rightarrow 00:34:28.412$ So it turns out that and again some studies

NOTE Confidence: 0.935608953846154

 $00:34:28.412 \longrightarrow 00:34:30.891$ we did a few years ago back in 2014,

NOTE Confidence: 0.935608953846154

 $00{:}34{:}30{.}891 \dashrightarrow 00{:}34{:}33{.}046$ we showed that these mice

NOTE Confidence: 0.935608953846154

 $00:34:33.046 \rightarrow 00:34:34.339$ have normal strength.

NOTE Confidence: 0.935608953846154

 $00:34:34.340 \longrightarrow 00:34:36.060$ We had they have a lot of they,

- NOTE Confidence: 0.935608953846154
- $00:34:36.060 \rightarrow 00:34:38.970$ they have normal ability to recognize
- NOTE Confidence: 0.935608953846154
- $00{:}34{:}38{.}970 \dashrightarrow 00{:}34{:}41{.}450$ things in a remember things in a swim
- NOTE Confidence: 0.935608953846154
- $00{:}34{:}41{.}450 \dashrightarrow 00{:}34{:}43{.}615$ test when you do Morris water maze.
- NOTE Confidence: 0.935608953846154
- $00:34:43.620 \rightarrow 00:34:45.540$ But they're socially abnormal.
- NOTE Confidence: 0.935608953846154
- $00:34:45.540 \rightarrow 00:34:48.915$ And this is typical of mice that are
- NOTE Confidence: 0.935608953846154
- $00{:}34{:}48{.}915 \dashrightarrow 00{:}34{:}51{.}340$ believed to be in the human equivalent
- NOTE Confidence: 0.935608953846154
- $00:34:51.340 \rightarrow 00:34:53.340$ of the autism spectrum disorder,
- NOTE Confidence: 0.935608953846154
- $00:34:53.340 \rightarrow 00:34:56.940$ which as I said is part of the ARX phenotype.
- NOTE Confidence: 0.935608953846154
- $00{:}34{:}56{.}940 \dashrightarrow 00{:}34{:}58{.}796$ And so here the I'm just going to
- NOTE Confidence: 0.935608953846154
- $00:34:58.796 \rightarrow 00:35:00.202$ show you one socialization test
- NOTE Confidence: 0.935608953846154
- $00:35:00.202 \rightarrow 00:35:02.592$ we did where you you take this is
- NOTE Confidence: 0.935608953846154
- $00{:}35{:}02.592 \dashrightarrow 00{:}35{:}04.004$ called the novel mouse experiment
- NOTE Confidence: 0.935608953846154
- $00:35:04.004 \dashrightarrow 00:35:06.436$ and where you what you do is you
- NOTE Confidence: 0.935608953846154
- $00{:}35{:}06{.}436 \dashrightarrow 00{:}35{:}08{.}709$ put one mouse in this plexiglass
- NOTE Confidence: 0.935608953846154
- $00:35:08.709 \longrightarrow 00:35:10.614$ thing with these little holes.
- NOTE Confidence: 0.935608953846154

 $00:35:10.620 \longrightarrow 00:35:12.223$ And you put in the other side

NOTE Confidence: 0.935608953846154

 $00:35:12.223 \longrightarrow 00:35:14.069$ of it and either an empty one

NOTE Confidence: 0.935608953846154

 $00:35:14.069 \rightarrow 00:35:15.512$ of these or an inanimate object,

NOTE Confidence: 0.935608953846154

 $00:35:15.512 \longrightarrow 00:35:17.123$ you can put like a stuffed animal

NOTE Confidence: 0.935608953846154

 $00:35:17.123 \longrightarrow 00:35:18.497$ or something like that in it.

NOTE Confidence: 0.935608953846154

 $00:35:18.500 \dashrightarrow 00:35:20.460$ And this is the test mouse right here.

NOTE Confidence: 0.935608953846154

 $00:35:20.460 \dashrightarrow 00:35:23.020$ And this mouse has never seen this mouse.

NOTE Confidence: 0.935608953846154

 $00:35:23.020 \rightarrow 00:35:23.794$ They're social creatures.

NOTE Confidence: 0.935608953846154

 $00:35:23.794 \rightarrow 00:35:25.342$ They're going to go and interact

NOTE Confidence: 0.935608953846154

 $00:35:25.342 \longrightarrow 00:35:26.100$ with each other.

NOTE Confidence: 0.935608953846154

 $00:35:26.100 \longrightarrow 00:35:27.402$ And you can see that when you

NOTE Confidence: 0.935608953846154

 $00:35:27.402 \longrightarrow 00:35:28.499$ put in these novel mice,

NOTE Confidence: 0.935608953846154

 $00:35:28.500 \rightarrow 00:35:31.380$ the the blue bar shows you how much time,

NOTE Confidence: 0.935608953846154

 $00:35:31.380 \rightarrow 00:35:33.865$ the percent of time that they're spending

NOTE Confidence: 0.935608953846154

 $00:35:33.865 \rightarrow 00:35:36.249$ with that novel with that new mouse.

NOTE Confidence: 0.935608953846154

 $00:35:36.250 \rightarrow 00:35:38.770$ Whereas the mutants don't do that.

 $00{:}35{:}38{.}770 \dashrightarrow 00{:}35{:}40{.}429$ So they've got a socialization defect and

NOTE Confidence: 0.935608953846154

 $00:35:40.429 \rightarrow 00:35:42.288$ we showed that through several different,

NOTE Confidence: 0.935608953846154

 $00:35:42.290 \rightarrow 00:35:45.450$ but like I said this is just one of those.

NOTE Confidence: 0.9452852416666667

 $00:35:45.450 \rightarrow 00:35:47.808$ So coming back to this patterning,

NOTE Confidence: 0.9452852416666667

 $00{:}35{:}47{.}810 \dashrightarrow 00{:}35{:}49{.}826$ this was really interesting to us because

NOTE Confidence: 0.945285241666667

 $00{:}35{:}49{.}826 \dashrightarrow 00{:}35{:}52{.}142$ if you look at patterning dorsal ventral

NOTE Confidence: 0.9452852416666667

 $00{:}35{:}52{.}142 \dashrightarrow 00{:}35{:}54{.}629$ patterning in the spinal cord where it's

NOTE Confidence: 0.945285241666667

 $00{:}35{:}54{.}629 \dashrightarrow 00{:}35{:}58{.}082$ been best elucidated work by Tom Jessel

NOTE Confidence: 0.9452852416666667

 $00{:}35{:}58.082 \dashrightarrow 00{:}36{:}01.696$ and James Briscoe and others, many others.

NOTE Confidence: 0.9452852416666667

 $00{:}36{:}01{.}700 \dashrightarrow 00{:}36{:}04{.}148$ What what we now know is that there's

NOTE Confidence: 0.9452852416666667

 $00:36:04.148 \longrightarrow 00:36:06.784$ specific cell types that come from different

NOTE Confidence: 0.945285241666667

 $00{:}36{:}06{.}784 \dashrightarrow 00{:}36{:}08{.}739$ regions along the progenitor zone,

NOTE Confidence: 0.9452852416666667

 $00:36:08.740 \dashrightarrow 00:36:11.340$ from dorsal to ventral in the spinal cord,

NOTE Confidence: 0.9452852416666667

 $00{:}36{:}11{.}340 \dashrightarrow 00{:}36{:}15{.}076$ and that these are defined by Sonic hedgehog

NOTE Confidence: 0.9452852416666667

 $00{:}36{:}15.076$ --> $00{:}36{:}17.700$ expressed out of the noto cord and then

00:36:17.766 - 00:36:20.259 in the floor plate and on the roof plate,

NOTE Confidence: 0.9452852416666667

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

NOTE Confidence: 0.9452852416666667

 $00:36:21.880 \rightarrow 00:36:25.633$ and these both induce and repress.

NOTE Confidence: 0.9452852416666667

 $00:36:25.633 \rightarrow 00:36:27.766$ Different transcription factors,

NOTE Confidence: 0.945285241666667

 $00:36:27.770 \longrightarrow 00:36:30.590$ setting up these different domains

NOTE Confidence: 0.9452852416666667

 $00{:}36{:}30{.}590 \dashrightarrow 00{:}36{:}33{.}410$ along the dorsal ventral axis.

NOTE Confidence: 0.945285241666667

 $00{:}36{:}33{.}410 \dashrightarrow 00{:}36{.}36{.}186$ And the same thing seems to be happening

NOTE Confidence: 0.9452852416666667

 $00:36:36.186 \rightarrow 00:36:38.650$ in setting up different domains in

NOTE Confidence: 0.945285241666667

 $00{:}36{:}38.650 \dashrightarrow 00{:}36{:}40.770$ the cerebral cortex that define,

NOTE Confidence: 0.9452852416666667

 $00:36:40.770 \dashrightarrow 00:36:44.410$ as I mentioned before, where the thalamic,

NOTE Confidence: 0.9452852416666667

 $00:36:44.410 \rightarrow 00:36:45.301$ thalamic cortical projections

NOTE Confidence: 0.9452852416666667

 $00:36:45.301 \rightarrow 00:36:46.489$ are going to be.

NOTE Confidence: 0.9452852416666667

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

NOTE Confidence: 0.9452852416666667

 $00{:}36{:}48.010 \dashrightarrow 00{:}36{:}49.662$ visual cortex back here.

NOTE Confidence: 0.945285241666667

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

NOTE Confidence: 0.9452852416666667

 $00:36:51.730 \longrightarrow 00:36:53.170$ your sensory cortex.

 $00:36:53.170 \longrightarrow 00:36:55.570$ All of these primary cortices

NOTE Confidence: 0.9452852416666667

 $00{:}36{:}55{.}570 \dashrightarrow 00{:}36{:}58{.}029$ are coming out of definition,

NOTE Confidence: 0.9452852416666667

 $00{:}36{:}58{.}030 \dashrightarrow 00{:}37{:}00{.}046$ and that definition starts

NOTE Confidence: 0.9452852416666667

 $00:37:00.046 \rightarrow 00:37:03.510$ with these different gradients,

NOTE Confidence: 0.9452852416666667

 $00{:}37{:}03{.}510 \dashrightarrow 00{:}37{:}06{.}310$ first identified by Denis O'Leary

NOTE Confidence: 0.945285241666667

 $00:37:06.310 \longrightarrow 00:37:07.990$ and his group,

NOTE Confidence: 0.9452852416666667

 $00{:}37{:}07{.}990 \dashrightarrow 00{:}37{:}10{.}657$ that you get a gradient of different

NOTE Confidence: 0.945285241666667

 $00{:}37{:}10.657 \dashrightarrow 00{:}37{:}12.845$ factors that turn on different

NOTE Confidence: 0.9452852416666667

 $00{:}37{:}12.845 \dashrightarrow 00{:}37{:}15.265$ transcription factors in the brain,

NOTE Confidence: 0.9452852416666667

 $00{:}37{:}15{.}270 \dashrightarrow 00{:}37{:}18{.}721$ and it's the overlap of these different

NOTE Confidence: 0.9452852416666667

 $00:37:18.721 \longrightarrow 00:37:21.210$ patterns of these signaling molecules.

NOTE Confidence: 0.945285241666667

 $00{:}37{:}21{.}210 \dashrightarrow 00{:}37{:}23{.}710$ Turning on transcription factors that

NOTE Confidence: 0.9452852416666667

 $00:37:23.710 \rightarrow 00:37:26.786$ define these different regions of the brain,

NOTE Confidence: 0.945285241666667

 $00:37:26.790 \longrightarrow 00:37:27.023$ well,

NOTE Confidence: 0.945285241666667

 $00:37:27.023 \longrightarrow 00:37:28.654$ we had not actually been able to

 $00:37:28.654 \rightarrow 00:37:30.270$ find any transcription factors.

NOTE Confidence: 0.9452852416666667

 $00:37:30.270 \longrightarrow 00:37:32.028$ So we took a new approach,

NOTE Confidence: 0.945285241666667

 $00:37:32.030 \longrightarrow 00:37:33.682$ something called Samoa which

NOTE Confidence: 0.945285241666667

 $00:37:33.682 \rightarrow 00:37:35.747$ stands for single molecule assay.

NOTE Confidence: 0.945285241666667

 $00:37:35.750 \rightarrow 00:37:38.529$ And this is a highly sensitive methodology

NOTE Confidence: 0.9452852416666667

 $00{:}37{:}38{.}529 \dashrightarrow 00{:}37{:}41{.}975$ to be able to look at a single

NOTE Confidence: 0.9452852416666667

 $00:37:41.975 \longrightarrow 00:37:44.150$ molecules interacting with each other.

NOTE Confidence: 0.9452852416666667

 $00{:}37{:}44.150 \dashrightarrow 00{:}37{:}46.292$ And we had to build a transcription

NOTE Confidence: 0.9452852416666667

 $00:37:46.292 \longrightarrow 00:37:47.830$ factor library because one didn't

NOTE Confidence: 0.9452852416666667

 $00:37:47.830 \longrightarrow 00:37:49.225$ exist for just the brains,

NOTE Confidence: 0.9452852416666667

 $00:37:49.230 \longrightarrow 00:37:51.490$ we took all we actually.

NOTE Confidence: 0.9452852416666667

 $00:37:51.490 \longrightarrow 00:37:53.352$ We cloned into a library all the

NOTE Confidence: 0.9452852416666667

 $00{:}37{:}53{.}352 \dashrightarrow 00{:}37{:}54{.}431$ transcription factors that are

NOTE Confidence: 0.9452852416666667

 $00:37:54.431 \rightarrow 00:37:56.516$ 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: 0.9452852416666667

 $00:37:58.810 \longrightarrow 00:37:59.970$ And when we did that

- NOTE Confidence: 0.946962533333333
- $00:38:02.410 \longrightarrow 00:38:04.738$ we were able to find a number of
- NOTE Confidence: 0.946962533333333
- $00:38:04.738 \rightarrow 00:38:06.690$ different factor transcription factors.
- NOTE Confidence: 0.946962533333333
- $00:38:06.690 \dashrightarrow 00:38:08.334$ Now that interacted with arx and
- NOTE Confidence: 0.946962533333333
- $00:38:08.334 \rightarrow 00:38:10.372$ you can see they have overlapping
- NOTE Confidence: 0.946962533333333
- $00:38:10.372 \rightarrow 00:38:12.128$ patterns in different regions,
- NOTE Confidence: 0.946962533333333
- $00:38:12.130 \longrightarrow 00:38:14.650$ so some just in the cortex,
- NOTE Confidence: 0.946962533333333
- $00:38:14.650 \rightarrow 00:38:17.536$ others just in the ganglionic eminence.
- NOTE Confidence: 0.946962533333333
- $00:38:17.540 \longrightarrow 00:38:18.914$ And others that are both in
- NOTE Confidence: 0.946962533333333
- $00{:}38{:}18{.}914 \dashrightarrow 00{:}38{:}20{.}304$ the cortex and the ganglionic
- NOTE Confidence: 0.946962533333333
- 00:38:20.304 --> 00:38:21.980 eminence in different patterns.
- NOTE Confidence: 0.946962533333333
- 00:38:21.980 --> 00:38:24.311 So this one just like ARX stronger
- NOTE Confidence: 0.946962533333333
- $00:38:24.311 \longrightarrow 00:38:26.540$ in the more posterior brain,
- NOTE Confidence: 0.946962533333333
- $00{:}38{:}26{.}540 \dashrightarrow 00{:}38{:}29{.}140$ less so in the anterior.
- NOTE Confidence: 0.946962533333333
- $00{:}38{:}29{.}140 \dashrightarrow 00{:}38{:}31{.}820$ And when we take and look at these
- NOTE Confidence: 0.946962533333333
- $00:38:31.820 \longrightarrow 00:38:33.020$ different transcription factors,
- NOTE Confidence: 0.946962533333333

 $00:38:33.020 \rightarrow 00:38:34.777$ what we see is that the patterning,

NOTE Confidence: 0.946962533333333

 $00{:}38{:}34.780 \dashrightarrow 00{:}38{:}37.012$ the gene expression that define these

NOTE Confidence: 0.946962533333333

 $00:38:37.012 \rightarrow 00:38:39.700$ different regions in the brain is disrupted.

NOTE Confidence: 0.946962533333333

 $00:38:39.700 \longrightarrow 00:38:42.822$ So you can see here in the

NOTE Confidence: 0.946962533333333

 $00{:}38{:}42.822 \dashrightarrow 00{:}38{:}45.158$ ARX and it's a a loss.

NOTE Confidence: 0.946962533333333

 $00{:}38{:}45{.}158 \dashrightarrow 00{:}38{:}48{.}386$ Of your frontal cortex and a

NOTE Confidence: 0.946962533333333

 $00:38:48.386 \dashrightarrow 00:38:51.699$ expansion of the ventral cortex.

NOTE Confidence: 0.946962533333333

 $00:38:51.700 \rightarrow 00:38:56.576$ When we lose a RX and to try and then map,

NOTE Confidence: 0.946962533333333

 $00:38:56.580 \longrightarrow 00:38:58.659$ but we want to try and map,

NOTE Confidence: 0.946962533333333

00:38:58.660 --> 00:38:59.360 well, OK,

NOTE Confidence: 0.946962533333333

 $00:38:59.360 \longrightarrow 00:39:01.110$ these these regions are

NOTE Confidence: 0.946962533333333

 $00:39:01.110 \dashrightarrow 00:39:03.420$ abnormal and the behaviors abnormal.

NOTE Confidence: 0.946962533333333

 $00:39:03.420 \longrightarrow 00:39:05.100$ Can we connect those two?

NOTE Confidence: 0.946962533333333

 $00{:}39{:}05{.}100 \dashrightarrow 00{:}39{:}07{.}500$ So we wanted to look at the actual

NOTE Confidence: 0.946962533333333

00:39:07.500 --> 00:39:08.915 Axon trajectories from these

NOTE Confidence: 0.946962533333333

00:39:08.915 --> 00:39:10.415 different regions to strike,

- NOTE Confidence: 0.946962533333333
- $00:39:10.420 \longrightarrow 00:39:12.690$ start mapping that out and
- NOTE Confidence: 0.946962533333333
- $00:39:12.690 \longrightarrow 00:39:15.890$ so we can go into a mouse.
- NOTE Confidence: 0.946962533333333
- 00:39:15.890 00:39:17.954 And we can actually inject these
- NOTE Confidence: 0.946962533333333
- $00:39:17.954 \longrightarrow 00:39:19.716$ different tracers that go along
- NOTE Confidence: 0.946962533333333
- $00{:}39{:}19.716 \dashrightarrow 00{:}39{:}21.648$ axons are ones that cross axons.
- NOTE Confidence: 0.946962533333333
- $00{:}39{:}21.650 \dashrightarrow 00{:}39{:}23.290$ And when we do that,
- NOTE Confidence: 0.946962533333333
- 00:39:23.290 00:39:24.730 what you can see here in the sensory,
- NOTE Confidence: 0.946962533333333
- $00:39:24.730 \longrightarrow 00:39:26.490$ so this is Ventrilateral,
- NOTE Confidence: 0.946962533333333
- $00:39:26.490 \longrightarrow 00:39:28.250$ this is ventral posterior.
- NOTE Confidence: 0.946962533333333
- 00:39:28.250 --> 00:39:31.379 You can see the normal mapping of
- NOTE Confidence: 0.946962533333333
- $00:39:31.379 \rightarrow 00:39:33.946$ the ventral lateral from the brain.
- NOTE Confidence: 0.946962533333333
- $00:39:33.946 \dashrightarrow 00:39:36.682$ But here the ventral posterior despite
- NOTE Confidence: 0.946962533333333
- 00:39:36.682 --> 00:39:38.822 you having normal axons coming
- NOTE Confidence: 0.946962533333333
- $00:39:38.822 \rightarrow 00:39:40.366$ through the internal commissure,
- NOTE Confidence: 0.946962533333333
- $00:39:40.370 \longrightarrow 00:39:42.066$ sorry, the internal capsule.
- NOTE Confidence: 0.946962533333333

 $00:39:42.066 \rightarrow 00:39:44.610$ They don't go to ventral posterior.

NOTE Confidence: 0.946962533333333

 $00:39:44.610 \rightarrow 00:39:47.193$ So we can show very specific mapping

NOTE Confidence: 0.946962533333333

00:39:47.193 --> 00:39:49.271 abnormalities and then correlate those NOTE Confidence: 0.946962533333333

 $00:39:49.271 \rightarrow 00:39:51.075$ with these behavioral abnormalities

NOTE Confidence: 0.946962533333333

 $00:39:51.075 \longrightarrow 00:39:53.569$ that we're seeing in the brain.

NOTE Confidence: 0.946962533333333

00:39:53.570 --> 00:39:56.618 So we're going everywhere from the NOTE Confidence: 0.946962533333333

00:39:56.618 --> 00:39:58.466 molecular understanding of how the

NOTE Confidence: 0.946962533333333

 $00:39:58.466 \longrightarrow 00:40:00.899$ cortex is defined to how that sets

NOTE Confidence: 0.946962533333333

 $00{:}40{:}00{.}899 \dashrightarrow 00{:}40{:}02{.}694$ up projections and connections and

NOTE Confidence: 0.946962533333333

 $00{:}40{:}02.694 \dashrightarrow 00{:}40{:}04.768$ what that does for the behavior

NOTE Confidence: 0.946962533333333

 $00:40:04.768 \longrightarrow 00:40:07.048$ of the brain giving us a really a

NOTE Confidence: 0.946962533333333

 $00{:}40{:}07{.}050 \dashrightarrow 00{:}40{:}10{.}260$ view from behavior to the molecule.

NOTE Confidence: 0.946962533333333

 $00{:}40{:}10.260 \dashrightarrow 00{:}40{:}12.990$ In the brain and in these developmental

NOTE Confidence: 0.946962533333333

 $00:40:12.990 \longrightarrow 00:40:13.380$ disorders.

NOTE Confidence: 0.947441742857143

 $00:40:16.100 \rightarrow 00:40:17.857$ So that's some ongoing work we're doing.

NOTE Confidence: 0.947441742857143

 $00{:}40{:}17.860 \dashrightarrow 00{:}40{:}20.947$ And and now I want to shift a little

 $00:40:20.947 \longrightarrow 00:40:23.779$ bit in the last 15 minutes or so

NOTE Confidence: 0.947441742857143

 $00:40:23.780 \rightarrow 00:40:26.012$ and talk about some other relatively

NOTE Confidence: 0.947441742857143

 $00:40:26.012 \rightarrow 00:40:28.416$ new work we've been doing and that

NOTE Confidence: 0.947441742857143

 $00:40:28.416 \longrightarrow 00:40:31.340$ is related to these two brains.

NOTE Confidence: 0.947441742857143

 $00:40:31.340 \longrightarrow 00:40:34.460$ So I already told you about this or

NOTE Confidence: 0.947441742857143

 $00{:}40{:}34{.}460 \dashrightarrow 00{:}40{:}37{.}811$ showed you the brain of the ARX with an

NOTE Confidence: 0.947441742857143

 $00{:}40{:}37.811 \dashrightarrow 00{:}40{:}39.750$ alanine tract expansion where you have an.

NOTE Confidence: 0.947441742857143

 $00:40:39.750 \longrightarrow 00:40:43.278$ A structurally normal brain, but with

NOTE Confidence: 0.947441742857143

 $00:40:43.278 \rightarrow 00:40:45.630$ 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

 $00:40:50.256 \longrightarrow 00:40:52.494$ mild intellectual disabilities,

NOTE Confidence: 0.947441742857143

 $00{:}40{:}52{.}494 \dashrightarrow 00{:}40{:}56{.}224$ but a structurally normal brain.

NOTE Confidence: 0.947441742857143

 $00:40:56.230 \rightarrow 00:40:58.106$ 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

 $00{:}41{:}00{.}070 \dashrightarrow 00{:}41{:}01{.}947$ here in the thal amus and in the

 $00:41:01.947 \longrightarrow 00:41:03.550$ basal ganglia here in this one.

NOTE Confidence: 0.947441742857143

 $00:41:03.550 \longrightarrow 00:41:05.748$ And and that's typical of these disorders.

NOTE Confidence: 0.947441742857143

 $00{:}41{:}05{.}750 \dashrightarrow 00{:}41{:}09{.}758$ These are due to mitochondrial disorders.

NOTE Confidence: 0.947441742857143

 $00{:}41{:}09.760 \dashrightarrow 00{:}41{:}11.895$ So these are mitochondrial related

NOTE Confidence: 0.947441742857143

 $00{:}41{:}11.895 \dashrightarrow 00{:}41{:}14.402$ epilepsies and these have always been

NOTE Confidence: 0.947441742857143

 $00:41:14.402 \rightarrow 00:41:16.802$ 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

 $00:41:19.274 \longrightarrow 00:41:21.571$ 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

 $00:41:23.360 \longrightarrow 00:41:24.680$ If we could replace that,

NOTE Confidence: 0.947441742857143

 $00:41:24.680 \longrightarrow 00:41:26.675$ 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

 $00:41:28.423 \longrightarrow 00:41:30.479$ 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

 $00:41:32.572 \rightarrow 00:41:34.888$ maybe it's more complicated than that.

 $00{:}41{:}34{.}890 \dashrightarrow 00{:}41{:}37{.}018$ And so we first looked at the

NOTE Confidence: 0.947441742857143

 $00{:}41{:}37.018 \dashrightarrow 00{:}41{:}39.475$ literature and it turns out that a

NOTE Confidence: 0.947441742857143

 $00:41:39.475 \rightarrow 00:41:41.320$ significant percentage of kids that

NOTE Confidence: 0.947441742857143

 $00:41:41.320 \rightarrow 00:41:43.523$ have mitochondrial disorders have

NOTE Confidence: 0.947441742857143

 $00:41:43.523 \rightarrow 00:41:48.570$ either abnormal Eegs or frank epilepsy.

NOTE Confidence: 0.947441742857143

 $00{:}41{:}48.570 \dashrightarrow 00{:}41{:}51.895$ And so we started studying this and

NOTE Confidence: 0.947441742857143

 $00{:}41{:}51{.}895 \dashrightarrow 00{:}41{:}53{.}890$ we looked at both the excitatory and

NOTE Confidence: 0.947441742857143

 $00:41:53.890 \rightarrow 00:41:55.768$ inhibitory neurons because our prediction is,

NOTE Confidence: 0.947441742857143

 $00:41:55.770 \longrightarrow 00:41:57.774$ remember the inhibitory when you have

NOTE Confidence: 0.947441742857143

 $00:41:57.774 \longrightarrow 00:42:00.369$ a defect in the excitatory neurons,

NOTE Confidence: 0.947441742857143

 $00:42:00.370 \rightarrow 00:42:01.610$ the brains are structurally normal,

NOTE Confidence: 0.947441742857143

 $00{:}42{:}01{.}610 \dashrightarrow 00{:}42{:}04{.}928$ but with inhibitory neurons you get a.

NOTE Confidence: 0.947441742857143

 $00{:}42{:}04{.}930 \dashrightarrow 00{:}42{:}07{.}506$ Seizures and intellectual disabilities.

NOTE Confidence: 0.947441742857143

 $00{:}42{:}07{.}506 \dashrightarrow 00{:}42{:}12{.}112$ So on the left side we've labeled

NOTE Confidence: 0.947441742857143

 $00{:}42{:}12.112 \dashrightarrow 00{:}42{:}15.567$ migrating excitatory neurons in green,

 $00:42:15.570 \longrightarrow 00:42:18.210$ and then in red we've labeled

NOTE Confidence: 0.947441742857143

 $00:42:18.210 \longrightarrow 00:42:19.090$ their mitochondria.

NOTE Confidence: 0.947441742857143

 $00:42:19.090 \longrightarrow 00:42:21.498$ And what you can see is it migrates

NOTE Confidence: 0.947441742857143

 $00{:}42{:}21{.}498 \dashrightarrow 00{:}42{:}23{.}226$ across is that the mitochondria

NOTE Confidence: 0.947441742857143

 $00:42:23.226 \longrightarrow 00:42:25.836$ stay just in front of the cell body

NOTE Confidence: 0.947441742857143

 $00:42:25.836 \longrightarrow 00:42:27.607$ as it migrates all the way across,

NOTE Confidence: 0.947441742857143

 $00:42:27.610 \longrightarrow 00:42:28.602$ and we've mapped that.

NOTE Confidence: 0.947441742857143

 $00{:}42{:}28.602 \dashrightarrow 00{:}42{:}31.300$ At the top you can see a quantitation

NOTE Confidence: 0.947441742857143

 $00:42:31.300 \longrightarrow 00:42:32.510$ of that.

NOTE Confidence: 0.947441742857143

 $00:42:32.510 \longrightarrow 00:42:33.750$ But if you look at the of the,

NOTE Confidence: 0.947441742857143

 $00:42:33.750 \longrightarrow 00:42:34.054$ sorry,

NOTE Confidence: 0.947441742857143

 $00:42:34.054 \longrightarrow 00:42:36.486$ 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

 $00:42:38.262 \longrightarrow 00:42:39.670$ the mitochondria behave very

NOTE Confidence: 0.947441742857143

 $00:42:39.670 \longrightarrow 00:42:41.430$ differently in all of them.

NOTE Confidence: 0.947441742857143

00:42:41.430 --> 00:42:42.220 Inhibitory neurons,
$00:42:42.220 \rightarrow 00:42:44.590$ they move around through the cells.

NOTE Confidence: 0.947441742857143

 $00:42:44.590 \longrightarrow 00:42:45.570$ Sometimes they go up

NOTE Confidence: 0.947441742857143

 $00:42:45.570 \longrightarrow 00:42:46.550$ into the leading process,

NOTE Confidence: 0.947441742857143

00:42:46.550 --> 00:42:48.126 particularly at branch points,

NOTE Confidence: 0.947441742857143

 $00:42:48.126 \rightarrow 00:42:50.490$ sometimes they're behind the cell body

NOTE Confidence: 0.947441742857143

 $00:42:50.554 \rightarrow 00:42:52.668$ and sometimes they're in front of it.

NOTE Confidence: 0.947441742857143

 $00:42:52.670 \longrightarrow 00:42:53.270$ So there's this

NOTE Confidence: 0.95434236

 $00:42:55.910 \rightarrow 00:42:57.705$ tremendous dynamic movement in the

NOTE Confidence: 0.95434236

 $00{:}42{:}57.705 \dashrightarrow 00{:}42{:}59.500$ inhibitory neurons that you don't

NOTE Confidence: 0.95434236

 $00:42:59.562 \longrightarrow 00:43:01.147$ see in the excitatory neurons.

NOTE Confidence: 0.95434236

 $00:43:01.150 \longrightarrow 00:43:03.070$ And so to study this further,

NOTE Confidence: 0.95434236

 $00{:}43{:}03{.}070 \dashrightarrow 00{:}43{:}04{.}670$ so this is just observation,

NOTE Confidence: 0.95434236

 $00:43:04.670 \longrightarrow 00:43:06.790$ 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

 $00:43:09.335 \longrightarrow 00:43:12.170$ where we removed this Ant 1-2,

 $00:43:12.170 \longrightarrow 00:43:15.830$ this is a transporter of a TP.

NOTE Confidence: 0.95434236

 $00:43:15.830 \longrightarrow 00:43:17.930$ We also did it pharmacologically

NOTE Confidence: 0.95434236

 $00:43:17.930 \longrightarrow 00:43:19.190$ using boncretic acid,

NOTE Confidence: 0.95434236

 $00:43:19.190 \rightarrow 00:43:21.605$ which actually is an inhibitor of this

NOTE Confidence: 0.95434236

 $00{:}43{:}21.605 \dashrightarrow 00{:}43{:}23.526$ transporter or we used oligomycin,

NOTE Confidence: 0.95434236

 $00:43:23.526 \longrightarrow 00:43:26.527$ which is an inhibitor of the last

NOTE Confidence: 0.95434236

 $00:43:26.527 \rightarrow 00:43:29.297$ step in the oxidative phosphorylation.

NOTE Confidence: 0.95434236

 $00:43:29.300 \longrightarrow 00:43:30.540$ 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

 $00{:}43{:}32{.}540 \dashrightarrow 00{:}43{:}34{.}815$ to ensure that it wasn't just lycolysis.

NOTE Confidence: 0.95434236

 $00:43:34.820 \longrightarrow 00:43:35.876$ We blocked lycolysis.

NOTE Confidence: 0.95434236

 $00{:}43{:}35{.}876 \dashrightarrow 00{:}43{:}38{.}700$ 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

 $00:43:46.760 \longrightarrow 00:43:48.304$ whereas the inhibitory neuron

NOTE Confidence: 0.90250405

 $00:43:48.304 \rightarrow 00:43:50.234$ is required for is requires

NOTE Confidence: 0.90250405

 $00:43:50.234 \rightarrow 00:43:51.600$ 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
- $00:43:52.656 \rightarrow 00:43:53.360$ about that part again,
- NOTE Confidence: 0.90250405
- $00:43:53.360 \longrightarrow 00:43:56.466$ this has been published now if
- NOTE Confidence: 0.90250405
- $00:43:56.466 \rightarrow 00:43:59.160$ you look, let's see, let's.
- NOTE Confidence: 0.944566485714286
- $00:44:01.240 \rightarrow 00:44:02.717$ 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
- $00:44:11.320 \rightarrow 00:44:13.208$ I'm not going to be able to show
- NOTE Confidence: 0.914349101818182
- $00:44:13.208 \rightarrow 00:44:16.000$ 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
- $00{:}44{:}19{.}030 \dashrightarrow 00{:}44{:}22{.}352$ neurons and what you'd see is that
- NOTE Confidence: 0.914349101818182
- $00:44:22.352 \rightarrow 00:44:25.537$ that on the top, a normal one.
- NOTE Confidence: 0.914349101818182
- $00{:}44{:}25{.}537 \dashrightarrow 00{:}44{:}27{.}832$ These, these inhibitory neurons have
- NOTE Confidence: 0.914349101818182
- $00{:}44{:}27.832 \dashrightarrow 00{:}44{:}29.859$ 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
- $00{:}44{:}32.058 \dashrightarrow 00{:}44{:}34.290$ 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

 $00{:}44{:}36{.}696 \dashrightarrow 00{:}44{:}39{.}208$ oligomyc
in or when we do it with bancrecic

NOTE Confidence: 0.914349101818182

 $00:44:39.208 \rightarrow 00:44:41.379$ acid or when we do it genetically,

NOTE Confidence: 0.914349101818182

 $00:44:41.380 \rightarrow 00:44:43.459$ 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

 $00:44:48.203 \rightarrow 00:44:50.209$ and the cell actually turning around

NOTE Confidence: 0.914349101818182

 $00:44:50.209 \rightarrow 00:44:52.243$ and going backwards and going back

NOTE Confidence: 0.914349101818182

 $00:44:52.243 \rightarrow 00:44:54.168$ and forth and not branching as much.

NOTE Confidence: 0.914349101818182

 $00{:}44{:}54{.}168 \dashrightarrow 00{:}44{:}56{.}111$ And then if you look in the genetic

NOTE Confidence: 0.914349101818182

 $00{:}44{:}56{.}111 \dashrightarrow 00{:}44{:}57{.}707$ model where we actually are looking

NOTE Confidence: 0.914349101818182

 $00:44:57.707 \longrightarrow 00:44:59.229$ at the cells migrating up,

NOTE Confidence: 0.914349101818182

 $00:44:59.230 \longrightarrow 00:45:00.862$ you'll see a defect in those

NOTE Confidence: 0.914349101818182

 $00:45:00.862 \rightarrow 00:45:02.629$ cells going up into the cortex,

NOTE Confidence: 0.914349101818182

 $00:45:02.630 \rightarrow 00:45:06.068$ 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,

 $00:45:10.590 \longrightarrow 00:45:12.830$ we. So why do cells turn around?

NOTE Confidence: 0.914349101818182

 $00:45:12.830 \longrightarrow 00:45:14.380$ It turns out all epithelial

NOTE Confidence: 0.914349101818182

 $00:45:14.380 \longrightarrow 00:45:15.631$ cells are polarized, right?

NOTE Confidence: 0.914349101818182

 $00:45:15.631 \longrightarrow 00:45:16.594$ And they're polarized.

NOTE Confidence: 0.914349101818182

 $00{:}45{:}16{.}594 \dashrightarrow 00{:}45{:}19{.}228$ You have the nucleus and then you have the

NOTE Confidence: 0.914349101818182

 $00:45:19.230 \rightarrow 00:45:21.830$ MTOC, the microtubule organizing center.

NOTE Confidence: 0.914349101818182

 $00:45:21.830 \dashrightarrow 00:45:23.228$ It's also known as the centriole.

NOTE Confidence: 0.914349101818182

 $00:45:23.230 \longrightarrow 00:45:24.030$ In the dividing cell,

NOTE Confidence: 0.914349101818182

 $00:45:24.030 \longrightarrow 00:45:24.830$ it's the same thing.

NOTE Confidence: 0.914349101818182

 $00{:}45{:}24.830 \dashrightarrow 00{:}45{:}26.546$ It's where the microtubules are organized

NOTE Confidence: 0.914320166

 $00:45:29.030 \rightarrow 00:45:31.706$ as cells migrate that MTOC moves

NOTE Confidence: 0.914320166

 $00{:}45{:}31.706 \dashrightarrow 00{:}45{:}33.512$ out into the leading process and then

NOTE Confidence: 0.914320166

 $00{:}45{:}33{.}512 \dashrightarrow 00{:}45{:}35{.}306$ the nucleus gets pulled behind it.

NOTE Confidence: 0.914320166

 $00:45:35.310 \longrightarrow 00:45:37.390$ That's how they migrate out.

NOTE Confidence: 0.914320166

 $00:45:37.390 \longrightarrow 00:45:38.758$ But in these cells,

 $00:45:38.758 \longrightarrow 00:45:40.468$ when you lose the mitochondria,

NOTE Confidence: 0.914320166

 $00{:}45{:}40{.}470 \dashrightarrow 00{:}45{:}42{.}094$ you lose that polarization.

NOTE Confidence: 0.914320166

 $00:45:42.094 \rightarrow 00:45:44.530$ And both in the genetic model

NOTE Confidence: 0.914320166

 $00:45:44.601 \rightarrow 00:45:46.876$ 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

 $00:45:49.280 \rightarrow 00:45:51.160$ is found over the top of the nucleus

NOTE Confidence: 0.914320166

 $00:45:51.160 \rightarrow 00:45:52.837$ or sometimes even behind the nucleus,

NOTE Confidence: 0.914320166

 $00{:}45{:}52{.}840 \dashrightarrow 00{:}45{:}54{.}015$ and that's when those cells

NOTE Confidence: 0.914320166

 $00{:}45{:}54.015 \dashrightarrow 00{:}45{:}54.720$ are turning around.

NOTE Confidence: 0.914320166

 $00:45:54.720 \longrightarrow 00:45:57.751$ So you're losing the polar polarity that

NOTE Confidence: 0.914320166

 $00:45:57.751 \rightarrow 00:46:00.639$ a normal epithelial cell in a neuron has.

NOTE Confidence: 0.914320166

 $00:46:00.640 \longrightarrow 00:46:04.600$ And that's what we have found

NOTE Confidence: 0.914320166

 $00:46:04.600 \longrightarrow 00:46:06.268$ so more recently,

NOTE Confidence: 0.914320166

 $00{:}46{:}06{.}268 \dashrightarrow 00{:}46{:}10{.}160$ 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

 $00:46:11.946 \rightarrow 00:46:14.268$ 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
- $00{:}46{:}16{.}990 \dashrightarrow 00{:}46{:}19{.}636$ And it turns out that mitochondria are
- NOTE Confidence: 0.914320166
- $00{:}46{:}19.636 \dashrightarrow 00{:}46{:}21.989$ moved along using molecular motors,
- NOTE Confidence: 0.914320166
- $00:46:21.990 \rightarrow 00:46:24.549$ moved along microtubules.
- NOTE Confidence: 0.914320166
- $00{:}46{:}24.550 \dashrightarrow 00{:}46{:}26.950$ And so we started thinking about,
- NOTE Confidence: 0.914320166
- $00:46:26.950 \longrightarrow 00:46:27.634$ you know,
- NOTE Confidence: 0.914320166
- $00:46:27.634 \longrightarrow 00:46:29.782$ how could we disrupt that and
- NOTE Confidence: 0.914320166
- $00:46:29.782 \longrightarrow 00:46:32.006$ the way that the mitochondria
- NOTE Confidence: 0.914320166
- $00:46:32.006 \rightarrow 00:46:33.990$ attached these molecular motors,
- NOTE Confidence: 0.914320166
- $00:46:33.990 \rightarrow 00:46:36.684$ 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
- $00:46:41.390 \longrightarrow 00:46:43.958$ but the they they attached to
- NOTE Confidence: 0.914320166
- $00{:}46{:}43.958 \dashrightarrow 00{:}46{:}45.670$ the mitochondria using these.
- NOTE Confidence: 0.914320166
- $00:46:45.670 \rightarrow 00:46:46.470$ Adapter proteins,
- NOTE Confidence: 0.914320166

 $00{:}46{:}46{.}470 \dashrightarrow 00{:}46{:}49{.}270$ which are called mirror one and mirror

NOTE Confidence: 0.914320166

 $00{:}46{:}49{.}270 \dashrightarrow 00{:}46{:}52{.}070$ 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

 $00:46:55.686 \rightarrow 00:46:57.230$ expressed in the developing brain.

NOTE Confidence: 0.914320166

 $00{:}46{:}57{.}230 \dashrightarrow 00{:}46{:}59{.}785$ So we just focused on mirror one.

NOTE Confidence: 0.914320166

 $00{:}46{:}59{.}790 \dashrightarrow 00{:}47{:}02{.}790$ And so mirror one's the main adapter protein.

NOTE Confidence: 0.914320166

 $00:47:02.790 \longrightarrow 00:47:05.230$ And if we take a knockout mirror one,

NOTE Confidence: 0.914320166

 $00{:}47{:}05{.}230 \dashrightarrow 00{:}47{:}07{.}378$ 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

 $00:47:09.630 \longrightarrow 00:47:12.340$ 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

 $00{:}47{:}13.492 \dashrightarrow 00{:}47{:}14.932$ 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

 $00{:}47{:}16.580 \dashrightarrow 00{:}47{:}17.876$ are always out at the front

NOTE Confidence: 0.914320166

 $00:47:17.876 \longrightarrow 00:47:18.740$ of the leading process.

- NOTE Confidence: 0.914320166
- $00:47:18.740 \longrightarrow 00:47:21.140$ These cells are migrating up.
- NOTE Confidence: 0.914320166
- $00:47:21.140 \longrightarrow 00:47:23.280$ If you look at the when
- NOTE Confidence: 0.914320166
- $00:47:23.280 \longrightarrow 00:47:24.980$ we knock out mirror one,
- NOTE Confidence: 0.914320166
- $00{:}47{:}24.980 \dashrightarrow 00{:}47{:}27.284$ most of the time the mirror ones at
- NOTE Confidence: 0.914320166
- $00{:}47{:}27{.}284 \dashrightarrow 00{:}47{:}29{.}833$ the back of the nucleus and again
- NOTE Confidence: 0.914320166
- $00:47:29.833 \rightarrow 00:47:31.733$ these cells migrate out normally.
- NOTE Confidence: 0.914320166
- $00:47:31.740 \longrightarrow 00:47:33.498$ So it's not affecting their migration,
- NOTE Confidence: 0.914320166
- $00:47:33.500 \rightarrow 00:47:35.275$ it's just affecting the localization
- NOTE Confidence: 0.914320166
- $00{:}47{:}35{.}275 \dashrightarrow 00{:}47{:}36{.}340$ 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
- $00:47:38.340 \longrightarrow 00:47:41.328$ like you see here and here.
- NOTE Confidence: 0.914320166
- 00:47:41.330 --> 00:47:42.066 In contrast,
- NOTE Confidence: 0.914320166
- $00{:}47{:}42.066 \dashrightarrow 00{:}47{:}44.642$ when we look at the inhibitory neurons,
- NOTE Confidence: 0.914320166
- $00{:}47{:}44.650 \dashrightarrow 00{:}47{:}46.421$ we see that the the mitochondria
- NOTE Confidence: 0.914320166
- $00{:}47{:}46{.}421 \dashrightarrow 00{:}47{:}48{.}124$ all of a sudden just aggregate
- NOTE Confidence: 0.914320166

 $00:47:48.124 \longrightarrow 00:47:49.888$ 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

 $00:47:51.846 \rightarrow 00:47:53.498$ microscopy where we can actually

NOTE Confidence: 0.914320166

 $00:47:53.498 \longrightarrow 00:47:55.528$ get a better look at these cells.

NOTE Confidence: 0.914320166

 $00{:}47{:}55{.}530 \dashrightarrow 00{:}47{:}57{.}228$ Looking at the mitochondria we see

NOTE Confidence: 0.914320166

 $00:47:57.228 \longrightarrow 00:47:59.890$ not only is are they they stuck,

NOTE Confidence: 0.914320166

 $00{:}47{:}59{.}890 \dashrightarrow 00{:}48{:}02{.}370$ but they're also abnormal.

NOTE Confidence: 0.914320166

 $00:48:02.370 \longrightarrow 00:48:04.536$ They become very small and punctate

NOTE Confidence: 0.914320166

 $00{:}48{:}04{.}536 \dashrightarrow 00{:}48{:}06{.}865$ as opposed to being nice and

NOTE Confidence: 0.914320166

 $00:48:06.865 \longrightarrow 00:48:08.485$ long and sometimes branched.

NOTE Confidence: 0.914320166

00:48:08.490 --> 00:48:09.898 As you see here,

NOTE Confidence: 0.914320166

 $00{:}48{:}09{.}898 \dashrightarrow 00{:}48{:}12{.}650$ so this is the defects that we see.

NOTE Confidence: 0.914320166

 $00{:}48{:}12.650 \dashrightarrow 00{:}48{:}14.870$ And we also see the same

NOTE Confidence: 0.914320166

 $00:48:14.870 \longrightarrow 00:48:15.610$ polarization defects.

NOTE Confidence: 0.914320166

 $00{:}48{:}15.610 \dashrightarrow 00{:}48{:}17.283$ So we can look at the direction

NOTE Confidence: 0.914320166

 $00:48:17.283 \longrightarrow 00:48:18.831$ these cells are migrating and we

- NOTE Confidence: 0.914320166
- $00:48:18.831 \rightarrow 00:48:20.644$ this is just how we calculated it.

 $00:48:20.650 \longrightarrow 00:48:22.570$ 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

 $00{:}48{:}24{.}970 \dashrightarrow 00{:}48{:}26{.}850$ But when we quantitate this,

NOTE Confidence: 0.914320166

 $00{:}48{:}26.850 \dashrightarrow 00{:}48{:}28.272$ 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: 0.94081267777778

 $00:48:29.276 \longrightarrow 00:48:30.902$ that are going in the wrong

NOTE Confidence: 0.94081267777778

 $00{:}48{:}30{.}902 \dashrightarrow 00{:}48{:}32{.}374$ direction here. They're all supposed

NOTE Confidence: 0.94081267777778

 $00:48:32.374 \longrightarrow 00:48:34.210$ to be going north up this way.

NOTE Confidence: 0.935245477142857

 $00{:}48{:}36{.}680 \dashrightarrow 00{:}48{:}38{.}790$ And these mice are also

NOTE Confidence: 0.935245477142857

 $00:48:38.790 \longrightarrow 00:48:39.634$ behaviorally abnormal.

NOTE Confidence: 0.935245477142857

 $00:48:39.640 \longrightarrow 00:48:40.792$ So normally mice,

NOTE Confidence: 0.935245477142857

 $00:48:40.792 \longrightarrow 00:48:43.096$ if you put these little white

NOTE Confidence: 0.935245477142857

 $00:48:43.096 \longrightarrow 00:48:45.560$ pads like this one you see here,

NOTE Confidence: 0.935245477142857

 $00:48:45.560 \longrightarrow 00:48:47.839$ they build a nest out of it and

 $00:48:47.839 \rightarrow 00:48:49.792$ you can see the wild type mouse

NOTE Confidence: 0.935245477142857

 $00:48:49.792 \longrightarrow 00:48:51.450$ over there building this nice

NOTE Confidence: 0.935245477142857

 $00:48:51.450 \longrightarrow 00:48:53.514$ normal round nest that they use.

NOTE Confidence: 0.935245477142857

 $00:48:53.520 \longrightarrow 00:48:55.356$ 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

 $00:48:56.280 \rightarrow 00:48:58.400$ 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

 $00:49:01.760 \longrightarrow 00:49:03.237$ some tear it up a little more,

NOTE Confidence: 0.935245477142857

 $00:49:03.240 \longrightarrow 00:49:05.865$ but they don't make an organized nest.

NOTE Confidence: 0.935245477142857

 $00:49:05.870 \longrightarrow 00:49:09.410$ They also have a interesting

NOTE Confidence: 0.935245477142857

 $00:49:09.410 \longrightarrow 00:49:11.344$ behavioral phenotype where

NOTE Confidence: 0.935245477142857

 $00:49:11.344 \longrightarrow 00:49:14.428$ they they have a high anxiety.

NOTE Confidence: 0.935245477142857

 $00:49:14.430 \longrightarrow 00:49:17.374$ So the way you test anxiety in the

NOTE Confidence: 0.935245477142857

 $00:49:17.374 \rightarrow 00:49:20.354$ mouse is that normally a mouse if you

NOTE Confidence: 0.935245477142857

 $00:49:20.354 \rightarrow 00:49:23.940$ put it into a open field they're they

 $00:49:23.940 \rightarrow 00:49:27.068$ they'll explore the entire box okay.

NOTE Confidence: 0.935245477142857

 $00:49:27.068 \longrightarrow 00:49:30.416$ But if you if they have.

NOTE Confidence: 0.935245477142857

 $00:49:30.420 \longrightarrow 00:49:32.202$ What's thought to be anxiety and

NOTE Confidence: 0.935245477142857

 $00:49:32.202 \rightarrow 00:49:33.524$ again you know, anthropomorphosizing.

NOTE Confidence: 0.935245477142857

 $00:49:33.524 \longrightarrow 00:49:35.220$ 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

 $00{:}49{:}36.860 \dashrightarrow 00{:}49{:}39.220$ they will tend to stay outside of the

NOTE Confidence: 0.935245477142857

 $00:49:39.220 \rightarrow 00:49:41.660$ center and stay at the edges of the box.

NOTE Confidence: 0.935245477142857

 $00{:}49{:}41.660 \dashrightarrow 00{:}49{:}43.304$ And here's what our mice with

NOTE Confidence: 0.935245477142857

 $00:49:43.304 \longrightarrow 00:49:44.700$ mirror one mutations look like.

NOTE Confidence: 0.935245477142857

 $00{:}49{:}44{.}700 \dashrightarrow 00{:}49{:}47{.}787$ They stay at the outside of the box as

NOTE Confidence: 0.935245477142857

 $00{:}49{:}47.787 \dashrightarrow 00{:}49{:}50.819$ opposed to exploring the middle of the box.

NOTE Confidence: 0.935245477142857

 $00:49:50.820 \rightarrow 00:49:52.650$ The other thing that's quite interesting

NOTE Confidence: 0.935245477142857

 $00{:}49{:}52.650 \dashrightarrow 00{:}49{:}55.311$ 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,

 $00:49:56.700 \longrightarrow 00:49:58.708$ and this is a little more than an

NOTE Confidence: 0.935245477142857

 $00{:}49{:}58.708 \dashrightarrow 00{:}50{:}00{.}179$ elevated plus maze because the.

NOTE Confidence: 0.935245477142857

 $00:50:00.180 \longrightarrow 00:50:03.568$ The arms that go up and down

NOTE Confidence: 0.935245477142857

 $00:50:03.568 \rightarrow 00:50:05.033$ are actually enclosed,

NOTE Confidence: 0.935245477142857

 $00:50:05.033 \rightarrow 00:50:08.977$ whereas the ones that go sideways are open.

NOTE Confidence: 0.935245477142857

 $00{:}50{:}08{.}980 \dashrightarrow 00{:}50{:}09{.}484$ And once again,

NOTE Confidence: 0.935245477142857

 $00:50:09.484 \rightarrow 00:50:10.940$ if you look at a wild type mouse,

NOTE Confidence: 0.935245477142857

 $00:50:10.940 \longrightarrow 00:50:12.780$ it'll explore all of those.

NOTE Confidence: 0.935245477142857

 $00{:}50{:}12.780 \dashrightarrow 00{:}50{:}14.016$ But interestingly, these mice,

NOTE Confidence: 0.935245477142857

 $00:50:14.016 \rightarrow 00:50:16.579$ and this is a little different than anxiety.

NOTE Confidence: 0.935245477142857

 $00{:}50{:}16.580 \dashrightarrow 00{:}50{:}19.500$ This is thought to be kind of a

NOTE Confidence: 0.935245477142857

 $00{:}50{:}19{.}500 \dashrightarrow 00{:}50{:}21{.}020$ claustrophobia type phenotype.

NOTE Confidence: 0.935245477142857

 $00:50:21.020 \longrightarrow 00:50:22.802$ You see that they don't enter

NOTE Confidence: 0.935245477142857

 $00:50:22.802 \rightarrow 00:50:24.300$ that closed box at all,

NOTE Confidence: 0.935245477142857

 $00:50:24.300 \rightarrow 00:50:26.368$ They're anxious about entering

NOTE Confidence: 0.935245477142857

 $00{:}50{:}26{.}368 \dashrightarrow 00{:}50{:}27{.}919$ the closed arms.

- NOTE Confidence: 0.935245477142857
- $00{:}50{:}27{.}920 \dashrightarrow 00{:}50{:}28{.}572$ Of this,
- NOTE Confidence: 0.935245477142857
- $00:50:28.572 \rightarrow 00:50:30.528$ whereas the wild type go through
- NOTE Confidence: 0.935245477142857
- $00{:}50{:}30{.}528 \dashrightarrow 00{:}50{:}32{.}879$ 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
- $00{:}50{:}34.256 \dashrightarrow 00{:}50{:}39.204$ these behavioral defects and we think
- NOTE Confidence: 0.935245477142857
- $00:50:39.204 \rightarrow 00:50:41.314$ the brains are structurally normal,
- NOTE Confidence: 0.935245477142857
- $00{:}50{:}41{.}320 \dashrightarrow 00{:}50{:}43{.}090$ the brains of the kids are
- NOTE Confidence: 0.935245477142857
- $00:50:43.090 \rightarrow 00:50:43.680$ structurally normal.
- NOTE Confidence: 0.935245477142857
- $00:50:43.680 \longrightarrow 00:50:46.000$ They have these different
- NOTE Confidence: 0.935245477142857
- 00:50:46.000 00:50:47.160 behavioral phenotypes,
- NOTE Confidence: 0.935245477142857
- $00{:}50{:}47.160 \dashrightarrow 00{:}50{:}49.680$ they have epilepsy just like these mice do.
- NOTE Confidence: 0.92769987
- $00{:}50{:}53.070 \dashrightarrow 00{:}50{:}54.806$ And so we're now looking to see and
- NOTE Confidence: 0.92769987
- $00:50:54.806 \rightarrow 00:50:56.673$ and this is going to be the end of
- NOTE Confidence: 0.92769987
- $00{:}50{:}56{.}673 \dashrightarrow 00{:}50{:}58{.}119$ the story that we're looking to
- NOTE Confidence: 0.92769987
- $00{:}50{:}58{.}119 \dashrightarrow 00{:}50{:}59{.}715$ see what the connectivity is and
- NOTE Confidence: 0.92769987

 $00{:}50{:}59{.}715 \dashrightarrow 00{:}51{:}02{.}430$ what the changes in gene expression

NOTE Confidence: 0.92769987

 $00:51:02.430 \longrightarrow 00:51:04.242$ leading us to really think that

NOTE Confidence: 0.92769987

 $00:51:04.242 \rightarrow 00:51:06.026$ this epilepsy phenotype that you

NOTE Confidence: 0.92769987

 $00:51:06.026 \rightarrow 00:51:07.871$ have in the behavioral phenotype

NOTE Confidence: 0.92769987

 $00:51:07.871 \longrightarrow 00:51:09.830$ is not just an energy defect.

NOTE Confidence: 0.92769987

 $00:51:09.830 \rightarrow 00:51:12.050$ It's actually a neurodevelopmental

NOTE Confidence: 0.92769987

 $00{:}51{:}12.050 \dashrightarrow 00{:}51{:}14.825$ defect from these inhibitory neurons.

NOTE Confidence: 0.92769987

 $00:51:14.830 \longrightarrow 00:51:16.030$ And this is just a summation

NOTE Confidence: 0.92769987

 $00{:}51{:}16{.}030 \dashrightarrow 00{:}51{:}17{.}030$ diagram where you see the,

NOTE Confidence: 0.958942771428571

 $00:51:19.790 \longrightarrow 00:51:20.936$ the excitatory neurons,

NOTE Confidence: 0.958942771428571

 $00:51:20.936 \longrightarrow 00:51:22.464$ they migrate out normally.

NOTE Confidence: 0.958942771428571

 $00:51:22.470 \rightarrow 00:51:24.318$ We don't know that they function normally

NOTE Confidence: 0.958942771428571

 $00{:}51{:}24{.}318 \dashrightarrow 00{:}51{:}26{.}070$ with the with without mirror one,

NOTE Confidence: 0.958942771428571

 $00:51:26.070 \rightarrow 00:51:27.568$ but we know they migrate normally and

NOTE Confidence: 0.958942771428571

 $00:51:27.568 \rightarrow 00:51:29.388$ they form a structurally normal brain.

NOTE Confidence: 0.958942771428571

00:51:29.390 --> 00:51:31.250 But in contrast, these inhibitory

00:51:31.250 --> 00:51:33.110 neurons don't migrate out normally.

NOTE Confidence: 0.958942771428571

 $00{:}51{:}33{.}110 \dashrightarrow 00{:}51{:}34{.}720$ The mitochondria stay localized right

NOTE Confidence: 0.958942771428571

 $00:51:34.720 \longrightarrow 00:51:37.006$ at the front as opposed to distributing

NOTE Confidence: 0.958942771428571

 $00:51:37.006 \rightarrow 00:51:38.866$ in different parts of the cell.

NOTE Confidence: 0.958942771428571

 $00{:}51{:}38{.}870 \dashrightarrow 00{:}51{:}41{.}372$ And we actually have been able

NOTE Confidence: 0.958942771428571

 $00{:}51{:}41{.}372 \dashrightarrow 00{:}51{:}43{.}908$ to show that this is due to

NOTE Confidence: 0.958942771428571

 $00:51:43.910 \longrightarrow 00:51:46.310$ the the inhibitory neurons.

NOTE Confidence: 0.958942771428571

 $00:51:46.310 \longrightarrow 00:51:47.682$ They need mitochondria in

NOTE Confidence: 0.958942771428571

 $00:51:47.682 \longrightarrow 00:51:49.397$ the rear of the cell.

NOTE Confidence: 0.958942771428571

 $00{:}51{:}49{.}400 \dashrightarrow 00{:}51{:}53{.}075$ Because they require a separate type of.

NOTE Confidence: 0.958942771428571

 $00{:}51{:}53{.}080 \dashrightarrow 00{:}51{:}55{.}000$ It's kind of like thinking about

NOTE Confidence: 0.958942771428571

 $00{:}51{:}55{.}000 \dashrightarrow 00{:}51{:}56{.}899$ squeezing a tooth paste at the back.

NOTE Confidence: 0.958942771428571

 $00{:}51{:}56{.}899 \dashrightarrow 00{:}51{:}59{.}090$ They need that for their migration in

NOTE Confidence: 0.958942771428571

 $00{:}51{:}59{.}156 \dashrightarrow 00{:}52{:}01{.}599$ addition to the pulling from the front,

NOTE Confidence: 0.958942771428571

 $00{:}52{:}01{.}600 \dashrightarrow 00{:}52{:}03{.}030$ whereas the excitatory neurons don't

 $00:52:03.030 \longrightarrow 00:52:05.320$ seem to need that or as much of that.

NOTE Confidence: 0.92415216

 $00:52:07.480 \longrightarrow 00:52:10.717$ So let me end by just doing a

NOTE Confidence: 0.92415216

 $00:52:10.717 \longrightarrow 00:52:12.312$ brief summary and then thanking

NOTE Confidence: 0.92415216

 $00:52:12.312 \longrightarrow 00:52:13.997$ 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

 $00:52:17.546 \longrightarrow 00:52:19.316$ inner neurons might be involved.

NOTE Confidence: 0.92415216

 $00{:}52{:}19{.}320 \dashrightarrow 00{:}52{:}20{.}592$ In these different

NOTE Confidence: 0.92415216

00:52:20.592 --> 00:52:21.440 neurodevelopmental disabilities,

NOTE Confidence: 0.92415216

 $00{:}52{:}21{.}440 \dashrightarrow 00{:}52{:}24{.}072$ 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

 $00{:}52{:}26{.}121 \dashrightarrow 00{:}52{:}28{.}550$ 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

 $00{:}52{:}30{.}614 \dashrightarrow 00{:}52{:}32{.}844$ the behavioral defects and how

NOTE Confidence: 0.92415216

 $00{:}52{:}32{.}844 \dashrightarrow 00{:}52{:}35{.}074$ that affects these different mice.

NOTE Confidence: 0.92415216

 $00:52:35.080 \longrightarrow 00:52:37.754$ We begin to get new insights in

 $00:52:43.680 \longrightarrow 00:52:45.575$ to how these different defects

NOTE Confidence: 0.917715220833333

 $00:52:45.575 \longrightarrow 00:52:48.200$ led to new studies in terms of.

NOTE Confidence: 0.917715220833333

 $00:52:48.200 \longrightarrow 00:52:49.675$ What, how you might be

NOTE Confidence: 0.917715220833333

 $00:52:49.675 \longrightarrow 00:52:50.560$ treating these patients.

NOTE Confidence: 0.917715220833333

 $00{:}52{:}50{.}560 \dashrightarrow 00{:}52{:}52{.}648$ 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

 $00{:}52{:}54{.}760 \dashrightarrow 00{:}52{:}59{.}548$ we there there was identified a an

NOTE Confidence: 0.917715220833333

 $00:52:59.548 \longrightarrow 00:53:01.124$ estrogen related molecule that's

NOTE Confidence: 0.917715220833333

 $00{:}53{:}01{.}124 \dashrightarrow 00{:}53{:}03{.}178$ actually pretty effective for the

NOTE Confidence: 0.917715220833333

 $00{:}53{:}03{.}178 \dashrightarrow 00{:}53{:}05{.}238$ alanine tract expansion mouse mutants.

NOTE Confidence: 0.917715220833333

 $00{:}53{:}05{.}240 \dashrightarrow 00{:}53{:}07{.}544$ And Jeff Nobles and at Baylor gave this

NOTE Confidence: 0.917715220833333

 $00:53:07.544 \rightarrow 00:53:09.219$ estrogen to these mice and actually

NOTE Confidence: 0.917715220833333

 $00{:}53{:}09{.}219 \dashrightarrow 00{:}53{:}11{.}467$ did a very nice job at improving them

NOTE Confidence: 0.917715220833333

 $00{:}53{:}11{.}467 \dashrightarrow 00{:}53{:}13{.}679$ and that went into a clinical trial

NOTE Confidence: 0.917715220833333

 $00:53:13.679 \dashrightarrow 00:53:16.415$ which I actually don't know the results of.

 $00{:}53{:}16{.}420 \dashrightarrow 00{:}53{:}19{.}756$ 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

 $00:53:26.458 \longrightarrow 00:53:28.612$ And so you're specifically looking at

NOTE Confidence: 0.917715220833333

 $00:53:28.612 \rightarrow 00:53:30.655$ 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

 $00:53:36.199 \rightarrow 00:53:38.734$ opposed to the somatostatin subpopulations.

NOTE Confidence: 0.917715220833333

 $00{:}53{:}38{.}740 \dashrightarrow 00{:}53{:}40{.}676$ I also hope that I've given you a

NOTE Confidence: 0.917715220833333

 $00{:}53{:}40.676 \dashrightarrow 00{:}53{:}42.295$ little bit insight how different

NOTE Confidence: 0.917715220833333

 $00:53:42.295 \longrightarrow 00:53:44.670$ mutations in the same gene.

NOTE Confidence: 0.917715220833333

 $00{:}53{:}44.670 \dashrightarrow 00{:}53{:}47.190$ Can result in two different phenotypes.

NOTE Confidence: 0.917715220833333

 $00{:}53{:}47{.}190 \dashrightarrow 00{:}53{:}49{.}350$ So when you lose that gene you you affect

NOTE Confidence: 0.917715220833333

 $00{:}53{:}49{.}350 \dashrightarrow 00{:}53{:}51{.}430$ both excitatory and inhibitory neurons,

NOTE Confidence: 0.917715220833333

 $00:53:51.430 \longrightarrow 00:53:52.750$ at least for a RX,

NOTE Confidence: 0.917715220833333

 $00{:}53{:}52{.}750 \dashrightarrow 00{:}53{:}54{.}230$ whereas the alanine tract

- NOTE Confidence: 0.917715220833333
- $00:53:54.230 \rightarrow 00:53:56.450$ 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
- $00:53:58.590 \rightarrow 00:54:00.250$ giving you different phenotypes
- NOTE Confidence: 0.917715220833333
- $00:54:00.250 \longrightarrow 00:54:02.740$ in these different cell types and
- NOTE Confidence: 0.917715220833333
- $00{:}54{:}02.809 \dashrightarrow 00{:}54{:}04.789$ therefore different phenotypes.
- NOTE Confidence: 0.917715220833333
- $00{:}54{:}04.790 \dashrightarrow 00{:}54{:}05.402$ I've also,
- NOTE Confidence: 0.917715220833333
- $00:54:05.402 \rightarrow 00:54:06.626$ through the mitochondria work,
- NOTE Confidence: 0.917715220833333
- $00{:}54{:}06{.}630 \dashrightarrow 00{:}54{:}09{.}062$ talked about how metabolic
- NOTE Confidence: 0.917715220833333
- $00{:}54{:}09{.}062 \dashrightarrow 00{:}54{:}12{.}034$ perturbations in the inhibitory neurons.
- NOTE Confidence: 0.917715220833333
- $00:54:12.034 \rightarrow 00:54:14.398$ Because they require that
- NOTE Confidence: 0.917715220833333
- $00:54:14.398 \rightarrow 00:54:15.580$ oxidated phosphorylation,
- NOTE Confidence: 0.917715220833333
- $00{:}54{:}15{.}580 \dashrightarrow 00{:}54{:}17{.}358$ they no longer are able to function
- NOTE Confidence: 0.917715220833333
- $00{:}54{:}17{.}358 \dashrightarrow 00{:}54{:}19{.}190$ and I think this contributes to
- NOTE Confidence: 0.917715220833333
- $00{:}54{:}19{.}190 \dashrightarrow 00{:}54{:}20{.}870$ the phenotype in these patients
- NOTE Confidence: 0.917715220833333
- $00:54:20.870 \rightarrow 00:54:22.852$ and really should we should start
- NOTE Confidence: 0.917715220833333

 $00{:}54{:}22.852 \dashrightarrow 00{:}54{:}24.736$ thinking about new ways for the rapy

NOTE Confidence: 0.917715220833333

00:54:24.740 --> 00:54:27.890 as opposed to just trying to correct

NOTE Confidence: 0.917715220833333

 $00:54:27.890 \dashrightarrow 00:54:30.739$ the energetics in the brain itself.

NOTE Confidence: 0.917715220833333

 $00:54:30.740 \rightarrow 00:54:34.350$ So let me end there and really thank

NOTE Confidence: 0.917715220833333

 $00:54:34.350 \longrightarrow 00:54:36.180$ the people that have done this.

NOTE Confidence: 0.917715220833333

 $00{:}54{:}36{.}180 \dashrightarrow 00{:}54{:}38{.}328$ All the recent work on the marijuana

NOTE Confidence: 0.917715220833333

 $00:54:38.328 \longrightarrow 00:54:40.380$ has been done by a postdoc in my lab,

NOTE Confidence: 0.917715220833333

 $00:54:40.380 \longrightarrow 00:54:41.348$ Abby Myers,

NOTE Confidence: 0.917715220833333

 $00{:}54{:}41{.}348 \dashrightarrow 00{:}54{:}46{.}076$ who just now has a job as a as an

NOTE Confidence: 0.917715220833333

 $00:54:46.076 \rightarrow 00:54:48.216$ assistant professor at Hamilton College.

NOTE Confidence: 0.917715220833333

 $00{:}54{:}48.220 \dashrightarrow 00{:}54{:}51.124$ The work on the Alanine tract

NOTE Confidence: 0.917715220833333

 $00:54:51.124 \dashrightarrow 00:54:53.860$ expansion was done by AM DPHD

NOTE Confidence: 0.917715220833333

00:54:53.860 --> 00:54:57.288 student 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

 $00{:}54{:}58{.}720 \dashrightarrow 00{:}55{:}01{.}254$ All the epilepsy work is done in

NOTE Confidence: 0.917715220833333

 $00:55:01.254 \dashrightarrow 00:55:02.800$ collaboration with Eric Marsh,

 $00:55:02.800 \longrightarrow 00:55:04.800$ who was a postdoc in my lab and

NOTE Confidence: 0.917715220833333

 $00{:}55{:}04.800 \dashrightarrow 00{:}55{:}06.680$ we still collaborate together.

NOTE Confidence: 0.917715220833333

 $00{:}55{:}06{.}680 \dashrightarrow 00{:}55{:}10{.}886$ And the some of the other work I I

NOTE Confidence: 0.917715220833333

 $00:55:10.886 \dashrightarrow 00:55:13.439$ mentioned was done by Erica Lynn Hendel.

NOTE Confidence: 0.917715220833333

 $00{:}55{:}13.439 \dashrightarrow 00{:}55{:}16.637$ She did the early mitochondrial work

NOTE Confidence: 0.917715220833333

 $00{:}55{:}16.637 \dashrightarrow 00{:}55{:}20.157$ and all of this is supported and and

NOTE Confidence: 0.917715220833333

 $00:55:20.160 \longrightarrow 00:55:24.896$ 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

 $00{:}55{:}28.030 \dashrightarrow 00{:}55{:}29.390$ As they've been with me

NOTE Confidence: 0.917715220833333

 $00:55:29.390 \longrightarrow 00:55:30.750$ for a number of years.

NOTE Confidence: 0.917715220833333

 $00:55:30.750 \longrightarrow 00:55:32.080$ So with that I'll stop and I'm

NOTE Confidence: 0.917715220833333

 $00:55:32.080 \longrightarrow 00:55:33.309$ happy to take any questions.

NOTE Confidence: 0.917715220833333

 $00:55:33.310 \longrightarrow 00:55:34.670$ Thank you very much.

NOTE Confidence: 0.9301902

 $00{:}55{:}40.870 \dashrightarrow 00{:}55{:}41.350$ Yes,

NOTE Confidence: 0.9436080666666667

 $00:55:44.750 \longrightarrow 00:55:47.550$ didn't show any data,

- $00{:}55{:}47{.}550 \dashrightarrow 00{:}55{:}48{.}630$ but what about
- NOTE Confidence: 0.9402536
- $00{:}55{:}51{.}270 \dashrightarrow 00{:}55{:}51{.}430$ this
- NOTE Confidence: 0.9905706
- $00:55:53.590 \rightarrow 00:55:55.708$ polarization microphone may actually be
- NOTE Confidence: 0.87457219
- $00:55:59.270 \rightarrow 00:56:01.070$ that could affect migration?
- NOTE Confidence: 0.9179566666666667
- 00:56:02.120 --> 00:56:04.316 Yeah, yeah. So I you're right,
- NOTE Confidence: 0.91795666666666667
- $00:56:04.320 \longrightarrow 00:56:07.080$ I didn't show we we have done the
- NOTE Confidence: 0.9179566666666667
- $00{:}56{:}07{.}080 \dashrightarrow 00{:}56{:}08{.}982$ the energetics data looking at a
- NOTE Confidence: 0.9179566666666667
- $00{:}56{:}08{.}982 \dashrightarrow 00{:}56{:}10{.}952$ TP localization in the cell and
- NOTE Confidence: 0.9179566666666667
- $00{:}56{:}10.952 \dashrightarrow 00{:}56{:}12.557$ it's it's kind of interesting.
- NOTE Confidence: 0.9179566666666667
- $00:56:12.560 \rightarrow 00:56:13.540$ I'll come to your calcium
- NOTE Confidence: 0.9179566666666667
- $00:56:13.540 \longrightarrow 00:56:14.520$ question in just a second.
- NOTE Confidence: 0.9179566666666667
- 00:56:14.520 --> 00:56:15.896 It's actually very interesting.
- NOTE Confidence: 0.9179566666666667
- 00:56:15.896 --> 00:56:17.960 If you look at adult neurons,
- NOTE Confidence: 0.9179566666666667
- $00{:}56{:}17.960 \dashrightarrow 00{:}56{:}21.230$ mitochondria actually have to go out
- NOTE Confidence: 0.9179566666666667
- $00{:}56{:}21{.}230 \dashrightarrow 00{:}56{:}24{.}435$ into the into the processes of the
- NOTE Confidence: 0.9179566666666667
- $00:56:24.435 \rightarrow 00:56:26.930$ cell mostly the dendrites where new.

- NOTE Confidence: 0.9179566666666667
- $00:56:26.930 \rightarrow 00:56:28.602$ Synapses are being formed.
- NOTE Confidence: 0.9179566666666667
- $00{:}56{:}28.602 \dashrightarrow 00{:}56{:}30.692$ So synaptic plasticity is highly
- NOTE Confidence: 0.9179566666666667
- $00{:}56{:}30.692 \dashrightarrow 00{:}56{:}32.427$ dependent on mitochondria being
- NOTE Confidence: 0.9179566666666667
- $00{:}56{:}32{.}427 \dashrightarrow 00{:}56{:}34{.}517$ shuttled through this same mechanism
- NOTE Confidence: 0.9179566666666667
- $00{:}56{:}34{.}517 \dashrightarrow 00{:}56{:}36{.}725$ along with molecular motors out to
- NOTE Confidence: 0.9179566666666667
- $00{:}56{:}36{.}725 \dashrightarrow 00{:}56{:}39{.}038$ those sites and then they move back
- NOTE Confidence: 0.9179566666666667
- $00:56:39.038 \rightarrow 00:56:41.126$ as those synapses are being formed.
- NOTE Confidence: 0.9179566666666667
- $00{:}56{:}41{.}130 \dashrightarrow 00{:}56{:}41{.}490$ We think
- NOTE Confidence: 0.9402536
- $00{:}56{:}47.150 \dashrightarrow 00{:}56{:}48.560$ that's a similar defect the cell
- NOTE Confidence: 0.9402536
- $00:56:48.560 \longrightarrow 00:56:50.150$ and in your it isn't heard.
- NOTE Confidence: 0.9402536
- $00{:}56{:}50{.}150 \dashrightarrow 00{:}56{:}51{.}930$ I haven't I am showing we have done a little
- NOTE Confidence: 0.9402536
- $00{:}56{:}51{.}972 \dashrightarrow 00{:}56{:}53{.}505$ bit of calcium signaling on with this.
- NOTE Confidence: 0.9402536
- $00{:}56{:}53{.}510 \dashrightarrow 00{:}56{:}55{.}382$ We've done it more to look at the epilepsy
- NOTE Confidence: 0.9402536
- $00{:}56{:}55{.}382 \dashrightarrow 00{:}56{:}57{.}511$ and looking at the calcium waves for example
- NOTE Confidence: 0.9402536
- $00{:}56{:}57{.}511 \dashrightarrow 00{:}56{:}59{.}180$ in the hippocampus and in the cortex.
- NOTE Confidence: 0.9402536

 $00{:}56{:}59{.}180 \dashrightarrow 00{:}57{:}01{.}820$ And and there are significant abnormalities.

NOTE Confidence: 0.9402536

 $00{:}57{:}01{.}820 \dashrightarrow 00{:}57{:}04{.}230$ We have not yet looked at it in terms of

NOTE Confidence: 0.9402536

 $00:57:04.290 \longrightarrow 00:57:06.578$ intracellular localization of calcium,

NOTE Confidence: 0.9402536

 $00:57:06.580 \rightarrow 00:57:08.460$ which as you know is is a little bit harder.

NOTE Confidence: 0.9402536

 $00{:}57{:}08{.}460 \dashrightarrow 00{:}57{:}11{.}660$ But we that that is something I'd like to do,

NOTE Confidence: 0.9402536

 $00:57:11.660 \rightarrow 00:57:12.738$ 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

 $00:57:17.980 \rightarrow 00:57:24.164$ follow that, but the certain fact is that

NOTE Confidence: 0.9603804

 $00{:}57{:}24.164 \dashrightarrow 00{:}57{:}26.724$ underlying the sociability and anxiety.

NOTE Confidence: 0.9603804

 $00{:}57{:}26.730 \dashrightarrow 00{:}57{:}29.530$ 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

 $00{:}57{:}36{.}820 \dashrightarrow 00{:}57{:}39{.}222$ that we think So at least the one

NOTE Confidence: 0.9402536

 $00{:}57{:}39{.}222 \dashrightarrow 00{:}57{:}41{.}088$ circuit we have we think correlates

NOTE Confidence: 0.9402536

 $00:57:41.088 \rightarrow 00:57:43.325$ very nicely with some of the one of

NOTE Confidence: 0.9402536

 $00{:}57{:}43.325 \dashrightarrow 00{:}57{:}44.850$ the behavioral phenotypes that we have.

NOTE Confidence: 0.9352219

 $00:57:46.930 \longrightarrow 00:57:49.654$ When you look at these mice

- NOTE Confidence: 0.9352219
- $00:57:49.654 \rightarrow 00:57:52.150$ and the epilepsy we see a.

 $00{:}57{:}52{.}150 \dashrightarrow 00{:}57{:}54{.}448$ Simultaneous disorganization of

NOTE Confidence: 0.9352219

 $00:57:54.448 \longrightarrow 00:57:57.670$ electrical activity in in both

NOTE Confidence: 0.9352219

 $00:57:57.670 \rightarrow 00:57:59.510$ 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

 $00:58:03.011 \longrightarrow 00:58:05.537$ we put two frontal electrodes in

NOTE Confidence: 0.9352219

 $00:58:05.537 \rightarrow 00:58:07.829$ and two hippocampus electrodes in.

NOTE Confidence: 0.9352219

 $00:58:07.830 \longrightarrow 00:58:10.270$ So we're recording 4 sites

NOTE Confidence: 0.9352219

 $00:58:10.270 \rightarrow 00:58:12.600$ simultaneously in these mice and

NOTE Confidence: 0.9352219

 $00:58:12.600 \longrightarrow 00:58:14.450$ we see disorganization of the

NOTE Confidence: 0.9352219

 $00{:}58{:}14.450 \dashrightarrow 00{:}58{:}16.442$ cortex in and the hippocampus

NOTE Confidence: 0.9352219

 $00{:}58{:}16{.}442 \dashrightarrow 00{:}58{:}19{.}052$ in all areas and seizures can

NOTE Confidence: 0.9352219

 $00{:}58{:}19.052 \dashrightarrow 00{:}58{:}20.788$ come from different locations.

NOTE Confidence: 0.9352219

 $00{:}58{:}20.790 \dashrightarrow 00{:}58{:}22.785$ 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

- $00{:}58{:}25{.}400 \dashrightarrow 00{:}58{:}27{.}790$ disorganization of the of all the circuits.
- NOTE Confidence: 0.9402536
- 00:58:30.190 --> 00:58:30.510 Yeah,
- NOTE Confidence: 0.9654121
- $00:58:35.710 \longrightarrow 00:58:36.630$ yeah, absolutely.
- NOTE Confidence: 0.9402536
- $00{:}58{:}46{.}350 \dashrightarrow 00{:}58{:}46{.}710$ Yeah.
- NOTE Confidence: 0.6223776
- $00{:}58{:}54{.}210 \dashrightarrow 00{:}58{:}58{.}651$ Yeah, yeah. So we, we started to look
- NOTE Confidence: 0.6223776
- $00{:}58{:}58{.}651 \dashrightarrow 00{:}59{:}01{.}430$ at both fission and fusion and and
- NOTE Confidence: 0.6223776
- $00{:}59{:}01{.}430 \dashrightarrow 00{:}59{:}03{.}685$ unfortunately those experiments had fizzled.
- NOTE Confidence: 0.6223776
- $00:59:03.690 \longrightarrow 00:59:06.430$ So I don't have any data to
- NOTE Confidence: 0.6223776
- $00{:}59{:}06{.}430 \dashrightarrow 00{:}59{:}08{.}690$ 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
- $00:59:11.386 \dashrightarrow 00:59:12.810$ fission as opposed to a fusion.
- NOTE Confidence: 0.6223776
- $00:59:12.810 \longrightarrow 00:59:15.960$ We think they can break apart, but.
- NOTE Confidence: 0.6223776
- $00:59:15.960 \rightarrow 00:59:18.610$ When we've studied that, we've studied
- NOTE Confidence: 0.6223776
- $00{:}59{:}18.610 \dashrightarrow 00{:}59{:}21.400$ 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
- $00:59:23.696 \rightarrow 00:59:25.959$ try and disrupt that specifically.

- NOTE Confidence: 0.6223776
- 00:59:25.960 00:59:27.640 And so I don't think we,

 $00:59:27.640 \longrightarrow 00:59:29.158$ the cells get sick, they die,

NOTE Confidence: 0.6223776

 $00:59:29.160 \longrightarrow 00:59:30.516$ they don't move, they don't divide,

NOTE Confidence: 0.6223776

 $00:59:30.520 \longrightarrow 00:59:32.200$ they don't do a lot of things.

NOTE Confidence: 0.6223776

 $00:59:32.200 \longrightarrow 00:59:33.256$ And so that's been a really

NOTE Confidence: 0.6223776

 $00:59:33.256 \longrightarrow 00:59:34.359$ hard thing for us to study,

NOTE Confidence: 0.6223776

 $00:59:34.360 \longrightarrow 00:59:35.520$ at least in these neurons.

NOTE Confidence: 0.6223776

 $00{:}59{:}35{.}520 \dashrightarrow 00{:}59{:}38{.}240$ I know you can study it in other cell types,

NOTE Confidence: 0.6223776

 $00:59:38.240 \longrightarrow 00:59:40.207$ but when we try and introduce some

NOTE Confidence: 0.6223776

 $00:59:40.207 \rightarrow 00:59:42.070$ of those genes that are involved

NOTE Confidence: 0.6223776

 $00:59:42.070 \longrightarrow 00:59:43.996$ in both fission and fusion or

NOTE Confidence: 0.6223776

 $00{:}59{:}43.996 \dashrightarrow 00{:}59{:}46.156$ actually we've disrupted them. It is.

NOTE Confidence: 0.6223776

 $00:59:46.156 \rightarrow 00:59:48.460$ It is not gone very well for us.

NOTE Confidence: 0.6223776

 $00{:}59{:}48{.}460 \dashrightarrow 00{:}59{:}49{.}979$ So I wish I could answer that.

NOTE Confidence: 0.6223776

 $00:59:49.980 \longrightarrow 00:59:50.720$ We've tried.

 $00{:}59{:}50{.}720 \dashrightarrow 00{:}59{:}52{.}940$ It's a it's a great question

NOTE Confidence: 0.6223776

 $00{:}59{:}52{.}940 \dashrightarrow 00{:}59{:}54{.}256$ and I'd like to get an answer,

NOTE Confidence: 0.6223776

 $00:59:54.260 \longrightarrow 00:59:57.540$ 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

 $01:00:00.940 \longrightarrow 01:00:02.764$ totally something that

NOTE Confidence: 0.850692246

 $01:00:02.764 \rightarrow 01:00:05.084$ I'm told it got wrong.

NOTE Confidence: 0.850692246

 $01{:}00{:}05{.}084 \dashrightarrow 01{:}00{:}07{.}806$ So I'm really fascinated to try to

NOTE Confidence: 0.850692246

 $01:00:07.806 \longrightarrow 01:00:10.152$ connect with 1/3 of the dollars.

NOTE Confidence: 0.850692246

 $01{:}00{:}10.152 \dashrightarrow 01{:}00{:}12.240$ Seems like there is a rather

NOTE Confidence: 0.850692246

 $01:00:12.240 \longrightarrow 01:00:13.920$ 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

 $01:00:17.840 \longrightarrow 01:00:20.070$ just one basic question is

NOTE Confidence: 0.850692246

 $01:00:20.070 \longrightarrow 01:00:23.520$ that's the thing just seems

NOTE Confidence: 0.9603802925

 $01:00:25.920 \longrightarrow 01:00:27.680$ 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

 $01:00:36.612 \rightarrow 01:00:38.640$ 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
- $01:00:40.464 \longrightarrow 01:00:42.160$ together one, one part at a time.
- NOTE Confidence: 0.942266388
- $01:00:44.490 \longrightarrow 01:00:48.472$ In terms of the specificity, the behavior
- NOTE Confidence: 0.942266388
- $01:00:48.472 \dashrightarrow 01:00:52.327$ is actually becomes very specific.
- NOTE Confidence: 0.942266388
- $01:00:52.330 \longrightarrow 01:00:54.298$ Why can I say that? Well, we do,
- NOTE Confidence: 0.942266388
- $01{:}00{:}54.298 \dashrightarrow 01{:}00{:}56.370$ you do this whole battery of tests,
- NOTE Confidence: 0.942266388
- $01:00:56.370 \longrightarrow 01:00:57.418$ 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
- $01{:}00{:}59{.}039 \dashrightarrow 01{:}01{:}00{.}491$ marbles and things like that and
- NOTE Confidence: 0.942266388
- $01:01:00.491 \longrightarrow 01:01:02.447$ look at how fast they can find them.
- NOTE Confidence: 0.942266388
- $01:01:02.450 \longrightarrow 01:01:07.985$ You can do these memory tests you can do.
- NOTE Confidence: 0.942266388
- $01{:}01{:}07{.}990 \dashrightarrow 01{:}01{:}09{.}430$ You you have to test gate,
- NOTE Confidence: 0.942266388
- $01:01:09.430 \rightarrow 01:01:11.190$ 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
- $01:01:12.210 \longrightarrow 01:01:13.358$ or they can't walk, they don't,
- NOTE Confidence: 0.942266388

 $01:01:13.358 \rightarrow 01:01:14.506$ they can't do some of these things,

NOTE Confidence: 0.942266388

 $01:01:14.510 \longrightarrow 01:01:17.390$ they won't go over and see that other mouse.

NOTE Confidence: 0.942266388

 $01{:}01{:}17{.}390 \dashrightarrow 01{:}01{:}20{.}134$ So there's a whole battery of tests we

NOTE Confidence: 0.942266388

 $01:01:20.134 \rightarrow 01:01:22.592$ do and show that they're all normal.

NOTE Confidence: 0.942266388

 $01:01:22.592 \rightarrow 01:01:24.596$ I mean these mice behave normally

NOTE Confidence: 0.942266388

 $01:01:24.596 \longrightarrow 01:01:26.546$ in in almost all these tests,

NOTE Confidence: 0.942266388

 $01{:}01{:}26.550 \dashrightarrow 01{:}01{:}29.028$ but it gets very specific for these

NOTE Confidence: 0.942266388

 $01{:}01{:}29{.}028 \dashrightarrow 01{:}01{:}30{.}459$ socialization tests where we've

NOTE Confidence: 0.942266388

 $01{:}01{:}30{.}459 \dashrightarrow 01{:}01{:}33{.}197$ see all the defects. So the the,

NOTE Confidence: 0.942266388

 $01{:}01{:}33{.}197 \dashrightarrow 01{:}01{:}36{.}760$ 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

 $01:01:37.760 \longrightarrow 01:01:40.176$ is what does it mean? I mean,

NOTE Confidence: 0.942266388

 $01:01:40.176 \rightarrow 01:01:41.606$ that's the anthropomorphosizing, right?

NOTE Confidence: 0.942266388

 $01:01:41.606 \rightarrow 01:01:43.836$ 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

 $01:01:45.880 \rightarrow 01:01:49.520$ So we use these kind of surrogates

- NOTE Confidence: 0.942266388
- $01:01:49.520 \longrightarrow 01:01:52.640$ that the field has, has adopted to use.
- NOTE Confidence: 0.942266388
- $01{:}01{:}52.640 \dashrightarrow 01{:}01{:}55.680$ 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
- $01:01:56.680 \rightarrow 01:01:58.040$ a high degree of specificity.
- NOTE Confidence: 0.946962478333333
- 01:02:01.160 --> 01:02:02.219 2 questions. First,
- NOTE Confidence: 0.946962478333333
- $01{:}02{:}02{.}219 \dashrightarrow 01{:}02{:}04.888$ have you gone beyond the fact you
- NOTE Confidence: 0.946962478333333
- $01:02:04.888 \rightarrow 01:02:06.496$ 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
- $01{:}02{:}10{.}902 \dashrightarrow 01{:}02{:}12{.}346$ looking the downstream mechanism
- NOTE Confidence: 0.946962478333333
- $01:02:12.346 \longrightarrow 01:02:14.420$ and what are the gradients
- NOTE Confidence: 0.946962478333333
- $01:02:14.420 \longrightarrow 01:02:17.044$ there caused in migratory.
- NOTE Confidence: 0.946962478333333
- $01:02:17.044 \rightarrow 01:02:19.218$ 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
- $01{:}02{:}22.180 \dashrightarrow 01{:}02{:}25.180$ 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

 $01:02:32.370 \longrightarrow 01:02:35.050$ So we actually published.

NOTE Confidence: 0.930190133333333

 $01:02:35.050 \longrightarrow 01:02:35.876$ Several articles.

NOTE Confidence: 0.930190133333333

01:02:35.876 --> 01:02:37.808 They're all in J. Neuroscience.

NOTE Confidence: 0.930190133333333

 $01{:}02{:}37.808 \dashrightarrow 01{:}02{:}39.754$ Dan Lysco was a graduate student in

NOTE Confidence: 0.930190133333333

 $01:02:39.754 \longrightarrow 01:02:41.732$ my lab who was really interested in

NOTE Confidence: 0.930190133333333

 $01{:}02{:}41.732 \dashrightarrow 01{:}02{:}44.086$ this and and he started looking at

NOTE Confidence: 0.930190133333333

01:02:44.086 --> 01:02:45.470 gradients of different molecules

NOTE Confidence: 0.930190133333333

 $01{:}02{:}45{.}534 \dashrightarrow 01{:}02{:}47{.}580$ and their role in the migration

NOTE Confidence: 0.930190133333333

 $01{:}02{:}47.580 \dashrightarrow 01{:}02{:}49.876$ and actually connecting the

NOTE Confidence: 0.930190133333333

 $01:02:49.876 \longrightarrow 01:02:53.190$ gradients of different things,

NOTE Confidence: 0.930190133333333

 $01:02:53.190 \rightarrow 01:02:55.140$ particularly in the wind signaling

NOTE Confidence: 0.930190133333333

 $01:02:55.140 \longrightarrow 01:02:57.090$ pathway which is expressed

NOTE Confidence: 0.930190133333333

 $01{:}02{:}57{.}090 \dashrightarrow 01{:}03{:}00{.}978$ both in the meninges and in the

NOTE Confidence: 0.930190133333333

 $01:03:00.978 \longrightarrow 01:03:03.306$ that that migratory stream.

NOTE Confidence: 0.930190133333333

 $01:03:03.310 \rightarrow 01:03:06.154$ And show that that went signaling

NOTE Confidence: 0.930190133333333

 $01:03:06.154 \rightarrow 01:03:08.625$ going through the receptors through

- NOTE Confidence: 0.930190133333333
- $01:03:08.625 \rightarrow 01:03:10.613$ the frizzled receptors actually
- NOTE Confidence: 0.930190133333333
- $01{:}03{:}10.613 \dashrightarrow 01{:}03{:}14.111$ connects to the micro to the both
- NOTE Confidence: 0.930190133333333
- $01:03:14.111 \rightarrow 01:03:15.922$ actin and microtubule cytoskeleton
- NOTE Confidence: 0.930190133333333
- $01:03:15.922 \longrightarrow 01:03:18.806$ and affects the ability of that to
- NOTE Confidence: 0.930190133333333
- $01:03:18.806 \rightarrow 01:03:21.070$ branch and do things in the migration.
- NOTE Confidence: 0.921062423
- $01:03:27.990 \longrightarrow 01:03:31.448$ So, so that and. And also the
- NOTE Confidence: 0.921062423
- $01:03:31.448 \longrightarrow 01:03:34.698$ the other one actually that he
- NOTE Confidence: 0.921062423
- $01{:}03{:}34.698 \dashrightarrow 01{:}03{:}38.920$ studied even more was SD F4 and so
- NOTE Confidence: 0.93466282222222
- $01{:}03{:}42{.}160 \dashrightarrow 01{:}03{:}45{.}104$ CDCX CR4 and CX CL12 which is the
- NOTE Confidence: 0.93466282222222
- $01:03:45.104 \rightarrow 01:03:47.436$ ligand and he was able to show
- NOTE Confidence: 0.93466282222222
- $01:03:47.436 \longrightarrow 01:03:49.358$ that those are modulated by a RX.
- NOTE Confidence: 0.943128857142857
- $01{:}03{:}52{.}000 \dashrightarrow 01{:}03{:}53{.}519$ We haven't looked at all at synaptic,
- NOTE Confidence: 0.943128857142857
- $01:03:53.520 \longrightarrow 01:03:54.955$ it would be another area to go,
- NOTE Confidence: 0.943128857142857
- $01:03:54.960 \rightarrow 01:03:57.320$ but we have not done that, yeah.
- NOTE Confidence: 0.93019015
- $01{:}04{:}01{.}560 \dashrightarrow 01{:}04{:}05{.}000$ Look at the difference that make this
- NOTE Confidence: 0.9503169

- $01:04:07.040 \longrightarrow 01:04:11.080$ thing to run out or in
- NOTE Confidence: 0.9335445966666667
- 01:04:14.000 --> 01:04:14.879 human and so
- NOTE Confidence: 0.948304255
- $01:04:17.840 \rightarrow 01:04:21.008$ we've kind of we've done descriptive
- NOTE Confidence: 0.948304255
- $01:04:21.008 \rightarrow 01:04:24.572$ pathology in the human and we've been able
- NOTE Confidence: 0.948304255
- $01{:}04{:}24{.}572 \dashrightarrow 01{:}04{:}28{.}068$ to look at 2 humans with a RX mutations.
- NOTE Confidence: 0.948304255
- $01:04:28.070 \longrightarrow 01:04:29.918$ And they do have a deficit in
- NOTE Confidence: 0.948304255
- $01:04:29.918 \longrightarrow 01:04:31.126$ the inhibitory neurons that's
- NOTE Confidence: 0.948304255
- $01:04:31.126 \rightarrow 01:04:32.906$ 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
- $01:04:34.950 \rightarrow 01:04:36.988$ both had the Liz encephalophenotype.
- NOTE Confidence: 0.948304255
- $01{:}04{:}36{.}990 \dashrightarrow 01{:}04{:}39{.}160$ So they also had a, a structural defect.
- NOTE Confidence: 0.948304255
- $01:04:39.160 \longrightarrow 01:04:42.310$ So it wasn't so easy to parse that out.
- NOTE Confidence: 0.948304255
- $01:04:42.310 \longrightarrow 01:04:43.590$ 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
- $01:04:45.110 \longrightarrow 01:04:46.268$ We have not been able to,
- NOTE Confidence: 0.948304255
- $01:04:46.270 \rightarrow 01:04:48.722$ we've not done anything in the humans in
- NOTE Confidence: 0.948304255
- $01:04:48.722 \rightarrow 01:04:50.864$ terms of trying to study the migration,
- NOTE Confidence: 0.948304255
- $01{:}04{:}50.870 \dashrightarrow 01{:}04{:}52.910$ but we'd like to do that.
- NOTE Confidence: 0.948304255
- $01{:}04{:}52{.}910 \dashrightarrow 01{:}04{:}57{.}102$ And just recently, I've gotten 2 patients.
- NOTE Confidence: 0.948304255
- $01:04:57.102 \rightarrow 01:04:59.326$ They're they're actually brothers
- NOTE Confidence: 0.948304255
- $01{:}04{:}59{.}326 \dashrightarrow 01{:}05{:}02{.}580$ that have a RX mutations.
- NOTE Confidence: 0.948304255
- $01{:}05{:}02.580 \dashrightarrow 01{:}05{:}04.458$ The parents have consented and we've
- NOTE Confidence: 0.948304255
- $01{:}05{:}04{.}458 \dashrightarrow 01{:}05{:}06{.}938$ gotten and we're in the process of making
- NOTE Confidence: 0.948304255
- $01:05:06.940 \rightarrow 01:05:09.580$ IPSC's from those ARX mutation patients,
- NOTE Confidence: 0.948304255
- $01{:}05{:}09{.}580 \dashrightarrow 01{:}05{:}12{.}140$ which are going to allow us to then
- NOTE Confidence: 0.948304255
- $01:05:12.140 \rightarrow 01:05:15.019$ look at the migration of those cells,
- NOTE Confidence: 0.948304255
- $01:05:15.020 \rightarrow 01:05:16.798$ 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
- $01{:}05{:}19{.}040 \dashrightarrow 01{:}05{:}21{.}075$ how do they behave when we differentiate
- NOTE Confidence: 0.948304255
- $01{:}05{:}21.075 \dashrightarrow 01{:}05{:}23.469$ them to inner neurons or excitatory neurons.
- NOTE Confidence: 0.948304255
- $01:05:23.470 \longrightarrow 01:05:25.504$ So that is the next step to kind of
- NOTE Confidence: 0.948304255

 $01{:}05{:}25{.}504 \dashrightarrow 01{:}05{:}27{.}323$ make that transition and understand

NOTE Confidence: 0.948304255

 $01:05:27.323 \rightarrow 01:05:29.627$ what's the relationship of these two,

NOTE Confidence: 0.948304255

 $01:05:29.630 \longrightarrow 01:05:30.264$ the humans.

NOTE Confidence: 0.948304255

 $01{:}05{:}30{.}264 \dashrightarrow 01{:}05{:}32{.}483$ So that's what we're doing right now

NOTE Confidence: 0.948304255

 $01{:}05{:}32{.}483 \dashrightarrow 01{:}05{:}34{.}590$ to do that and I'm excited to have

NOTE Confidence: 0.948304255

 $01{:}05{:}34{.}590 \dashrightarrow 01{:}05{:}36{.}150$ these two patients and grateful there

NOTE Confidence: 0.90374499

 $01{:}05{:}41{.}150 \dashrightarrow 01{:}05{:}44{.}732$ is some evidence. Yeah.

NOTE Confidence: 0.90374499

 $01:05:44.732 \longrightarrow 01:05:46.420$ So I think that's.

NOTE Confidence: 0.90374499

01:05:46.420 $\operatorname{-->}$ 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

 $01:05:50.367 \dashrightarrow 01:05:52.291$ 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

 $01{:}05{:}57{.}069 \dashrightarrow 01{:}05{:}59{.}939$ I think defines that there is a

NOTE Confidence: 0.90374499

 $01:05:59.939 \rightarrow 01:06:01.619$ subpopulation of the inhibitory

NOTE Confidence: 0.90374499

 $01:06:01.619 \longrightarrow 01:06:03.614$ neurons that are coming from

- NOTE Confidence: 0.90374499
- $01{:}06{:}03.614 \dashrightarrow 01{:}06{:}05.460$ the cortical ventricular zone.
- NOTE Confidence: 0.942998163636364
- $01{:}06{:}07{.}980 \dashrightarrow 01{:}06{:}09{.}744$ All the studies in mice don't
- NOTE Confidence: 0.942998163636364
- $01:06:09.744 \longrightarrow 01:06:11.260$ seem to have supported that.
- NOTE Confidence: 0.942998163636364
- $01:06:11.260 \rightarrow 01:06:12.860$ 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
- $01{:}06{:}29.880 \dashrightarrow 01{:}06{:}31.665$ And I do think that there are
- NOTE Confidence: 0.938576485
- $01:06:31.665 \longrightarrow 01:06:33.045$ 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
- $01:06:35.104 \rightarrow 01:06:36.328$ ipsc's and differentiating
- NOTE Confidence: 0.938576485
- $01{:}06{:}36{.}328 \dashrightarrow 01{:}06{:}37{.}960$ them along different lines,
- NOTE Confidence: 0.938576485
- $01{:}06{:}37{.}960 \dashrightarrow 01{:}06{:}40{.}120$ 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: 0.9570260466666667
- $01:06:44.040 \rightarrow 01:06:46.720$ any other questions? All right.
- NOTE Confidence: 0.9570260466666667

01:06:46.720 --> 01:06:47.995 Well, thank you very much.