WEBVTT

NOTE duration:"00:48:34"

NOTE recognizability:0.916

NOTE language:en-us

NOTE Confidence: 0.9402536

00:00:00.000 --> 00:00:00.440 Wait,

NOTE Confidence: 0.81935804

00:00:03.640 --> 00:00:05.080 okay, do I need to?

NOTE Confidence: 0.81935804

00:00:05.080 --> 00:00:07.240 Yes, I need to click that.

NOTE Confidence: 0.81935804

00:00:07.240 --> 00:00:11.240 But can you help because

NOTE Confidence: 0.81935804

00:00:11.240 --> 00:00:12.640 the mouse is over here.

NOTE Confidence: 0.81935804

00:00:12.640 --> 00:00:14.664 So I will first thank Alicia and thank

NOTE Confidence: 0.81935804

00:00:14.664 --> 00:00:16.102 Marina for that wonderful introduction

NOTE Confidence: 0.81935804

00:00:16.102 --> 00:00:18.235 and to all of you for being here.

NOTE Confidence: 0.81935804

00:00:18.235 --> 00:00:20.116 And it's really an honor to be here

NOTE Confidence: 0.81935804

00:00:20.116 --> 00:00:21.616 for the special lecture and just

NOTE Confidence: 0.81935804

00:00:21.616 --> 00:00:23.418 a pleasure to be here in general

NOTE Confidence: 0.81935804

00:00:23.418 --> 00:00:25.188 because so many of my colleagues and.

NOTE Confidence: 0.81935804

00:00:25.188 --> 00:00:25.992 Friends are here,

NOTE Confidence: 0.81935804

00:00:25.992 --> 00:00:27.937 and I've learned a ton already about

NOTE Confidence: 0.81935804

00:00:27.937 --> 00:00:29.629 all the research that's going on.

NOTE Confidence: 0.81935804

00:00:29.630 --> 00:00:31.630 Like just makes me want to spend another

NOTE Confidence: 0.81935804

00:00:31.630 --> 00:00:33.810 week or more hanging out more because

NOTE Confidence: 0.81935804

00:00:33.810 --> 00:00:35.430 this clearly wasn't enough time.

NOTE Confidence: 0.81935804

00:00:35.430 --> 00:00:36.123 But I am.

NOTE Confidence: 0.81935804

00:00:36.123 --> 00:00:37.509 I'm really excited to tell you

NOTE Confidence: 0.81935804

00:00:37.509 --> 00:00:38.948 about some of our work today.

NOTE Confidence: 0.81935804

00:00:38.950 --> 00:00:41.236 And as you just heard a little bit from

NOTE Confidence: 0.81935804

00:00:41.236 --> 00:00:43.387 the background in the introduction,

NOTE Confidence: 0.81935804

00:00:43.390 --> 00:00:44.106 you know,

NOTE Confidence: 0.81935804

00:00:44.106 --> 00:00:46.254 I think is increasing evidence that

NOTE Confidence: 0.81935804

00:00:46.254 --> 00:00:47.814 really suggests that brain development

NOTE Confidence: 0.81935804

00:00:47.814 --> 00:00:49.990 is impaired in a lot of mental illnesses,

NOTE Confidence: 0.81935804

00:00:49.990 --> 00:00:51.850 including schizophrenia and bipolar.

NOTE Confidence: 0.81935804

00:00:51.850 --> 00:00:53.245 But you know,

NOTE Confidence: 0.81935804

00:00:53.250 --> 00:00:55.056 we know this is potentially happening

NOTE Confidence: 0.81935804

00:00:55.056 --> 00:00:56.929 long before the onset of symptoms,

NOTE Confidence: 0.81935804

00:00:56.930 --> 00:00:59.090 but there are many questions

NOTE Confidence: 0.81935804

00:00:59.090 --> 00:01:01.286 and challenges for the field in

NOTE Confidence: 0.81935804

00:01:01.286 --> 00:01:03.210 particular when do things begin?

NOTE Confidence: 0.81935804

00:01:03.210 --> 00:01:04.820 This is a major question as a

NOTE Confidence: 0.81935804

00:01:04.820 --> 00:01:05.784 developmental neurobiologist and glial

NOTE Confidence: 0.81935804

00:01:05.784 --> 00:01:07.408 biologist that I've been long interested in.

NOTE Confidence: 0.81935804

00:01:07.410 --> 00:01:09.186 It's just going back in development

NOTE Confidence: 0.81935804

00:01:09.186 --> 00:01:10.370 and trying to understand

NOTE Confidence: 0.81935804

00:01:10.370 --> 00:01:12.450 when and also which circuits.

NOTE Confidence: 0.81935804

00:01:12.450 --> 00:01:14.178 And ultimately the biggest question of

NOTE Confidence: 0.81935804

00:01:14.178 --> 00:01:16.778 course is what are the mechanisms and with

NOTE Confidence: 0.81935804

00:01:16.778 --> 00:01:19.530 emerging genetics of the last decade or more,

NOTE Confidence: 0.81935804

00:01:19.530 --> 00:01:20.364 that's really.

NOTE Confidence: 0.81935804

00:01:20.364 --> 00:01:23.283 Exploded in the field and it's really

NOTE Confidence: 0.81935804

00:01:23.283 --> 00:01:25.127 illuminating a lot of potential

NOTE Confidence: 0.81935804

00:01:25.127 --> 00:01:27.167 pathways that we never had before.

NOTE Confidence: 0.81935804

00:01:27.170 --> 00:01:29.294 It turns out genetics are pointing to a lot

NOTE Confidence: 0.81935804

00:01:29.294 --> 00:01:31.684 of a variance in genes that are implicating,

NOTE Confidence: 0.81935804

00:01:31.690 --> 00:01:32.428 not surprisingly,

NOTE Confidence: 0.81935804

00:01:32.428 --> 00:01:35.011 the synops right the point of communication

NOTE Confidence: 0.81935804

00:01:35.011 --> 00:01:36.990 between neurons where of course if

NOTE Confidence: 0.81935804

00:01:36.990 --> 00:01:38.170 synopses aren't working properly,

NOTE Confidence: 0.81935804

00:01:38.170 --> 00:01:40.411 that's going to have all kinds of impact on

NOTE Confidence: 0.81935804

00:01:40.411 --> 00:01:42.650 brain development and circuits and behavior.

NOTE Confidence: 0.81935804

00:01:42.650 --> 00:01:44.162 But the other thing I want

NOTE Confidence: 0.81935804

00:01:44.162 --> 00:01:45.170 to highlight today is,

NOTE Confidence: 0.81935804

00:01:45.170 --> 00:01:46.130 you know with all of the,

NOTE Confidence: 0.81935804

00:01:46.130 --> 00:01:46.460 the,

NOTE Confidence: 0.81935804

00:01:46.460 --> 00:01:48.770 the define mapping and GWA studies in,

NOTE Confidence: 0.81935804

00:01:48.770 --> 00:01:50.225 in the context of schizophrenia

NOTE Confidence: 0.81935804

00:01:50.225 --> 00:01:50.807 in particular,

NOTE Confidence: 0.81935804

00:01:50.810 --> 00:01:53.127 where I'll focus a bit more today,

NOTE Confidence: 0.81935804

00:01:53.130 --> 00:01:55.338 there's both common variants and rare

NOTE Confidence: 0.81935804

00:01:55.338 --> 00:01:57.605 variants that are implicating not just

NOTE Confidence: 0.81935804

00:01:57.605 --> 00:01:59.450 generally synapses but specific genes,

NOTE Confidence: 0.81935804

00:01:59.450 --> 00:02:01.700 not just variants but specific

NOTE Confidence: 0.81935804

00:02:01.700 --> 00:02:03.610 genes and which also,

NOTE Confidence: 0.81935804

00:02:03.610 --> 00:02:04.730 you know,

NOTE Confidence: 0.81935804

00:02:04.730 --> 00:02:07.145 implicate another pathway or part of the

NOTE Confidence: 0.81935804

00:02:07.145 --> 00:02:09.330 the body which is the immune system,

NOTE Confidence: 0.81935804

00:02:09.330 --> 00:02:09.610 which.

NOTE Confidence: 0.81935804

00:02:09.610 --> 00:02:11.570 At the beginning was a bit mysterious

NOTE Confidence: 0.81935804

00:02:11.570 --> 00:02:12.809 why these immune molecules

NOTE Confidence: 0.81935804

00:02:12.809 --> 00:02:14.675 keep coming up in the genetics,

NOTE Confidence: 0.81935804

00:02:14.680 --> 00:02:16.556 but I hope to convince you today

NOTE Confidence: 0.81935804

00:02:16.556 --> 00:02:18.368 that some same genes that relate

NOTE Confidence: 0.81935804

00:02:18.368 --> 00:02:19.636 to the immune system,

NOTE Confidence: 0.81935804

00:02:19.640 --> 00:02:21.810 like complement C4 and another

NOTE Confidence: 0.81935804

00:02:21.810 --> 00:02:23.320 gene called CSM D1.

NOTE Confidence: 0.81935804

00:02:23.320 --> 00:02:23.960 Ironically enough,

NOTE Confidence: 0.81935804

00:02:23.960 --> 00:02:25.880 my lab had been studying these

NOTE Confidence: 0.81935804

00:02:25.943 --> 00:02:27.628 genes independent of knowing the

NOTE Confidence: 0.81935804

00:02:27.628 --> 00:02:29.625 genetics was going to point to

NOTE Confidence: 0.81935804

00:02:29.625 --> 00:02:31.119 them in the context of risk,

NOTE Confidence: 0.81935804

00:02:31.120 --> 00:02:33.576 and so it's been a really great example

NOTE Confidence: 0.81935804

00:02:33.576 --> 00:02:35.679 where genetics and biology can converge.

NOTE Confidence: 0.81935804

00:02:35.680 --> 00:02:37.794 But even still to try to understand

NOTE Confidence: 0.81935804

00:02:37.794 --> 00:02:39.402 the mechanism requires a lot of

NOTE Confidence: 0.81935804

00:02:39.402 --> 00:02:40.900 work to try to develop new tools

NOTE Confidence: 0.931967356666666

00:02:40.952 --> 00:02:42.920 and importantly new model systems because

NOTE Confidence: 0.931967356666666

00:02:42.920 --> 00:02:45.400 even with the genetic leads and even with

NOTE Confidence: 0.931967356666666

00:02:45.400 --> 00:02:47.440 some biological insight as Marina just said.

NOTE Confidence: 0.931967356666666

00:02:47.440 --> 00:02:50.240 How do we translate that into new biomarkers,

NOTE Confidence: 0.931967356666666

00:02:50.240 --> 00:02:52.155 new mechanistic biomarkers that will

NOTE Confidence: 0.931967356666666

00:02:52.155 --> 00:02:54.637 enable us to stratify patients and to

NOTE Confidence: 0.931967356666666

00:02:54.637 --> 00:02:56.653 be able to identify those that are at

NOTE Confidence: 0.931967356666666

00:02:56.710 --> 00:02:58.996 more risk really in development ideally,

NOTE Confidence: 0.931967356666666

00:02:59.000 --> 00:03:00.530 but also new targets of

NOTE Confidence: 0.931967356666666

00:03:00.530 --> 00:03:01.754 intervention like that is,

NOTE Confidence: 0.931967356666666

00:03:01.760 --> 00:03:04.478 is you know I think it's a challenge but.

NOTE Confidence: 0.931967356666666

00:03:04.480 --> 00:03:06.587 I hope to convince you today through

NOTE Confidence: 0.931967356666666

00:03:06.587 --> 00:03:08.652 collaborative efforts by many of me and my

NOTE Confidence: 0.931967356666666

00:03:08.652 --> 00:03:10.479 colleagues at the broad and the Stanley

NOTE Confidence: 0.931967356666666

00:03:10.479 --> 00:03:12.477 Center and and many collaborators outside.

NOTE Confidence: 0.931967356666666

00:03:12.480 --> 00:03:14.352 We are trying to work together to try

NOTE Confidence: 0.931967356666666

00:03:14.352 --> 00:03:16.513 to to develop a pipeline to be able

NOTE Confidence: 0.931967356666666

00:03:16.513 --> 00:03:18.644 to take gene variant all the way to

NOTE Confidence: 0.931967356666666

00:03:18.644 --> 00:03:21.056 pathway to function so that we can try

NOTE Confidence: 0.931967356666666

00:03:21.056 --> 00:03:23.396 to develop new mechanistic understanding.

NOTE Confidence: 0.931967356666666

00:03:23.400 --> 00:03:24.870 So as a developmental neurobiologist

NOTE Confidence: 0.931967356666666

00:03:24.870 --> 00:03:27.412 and I think back to when I was a

NOTE Confidence: 0.931967356666666

00:03:27.412 --> 00:03:29.279 graduate student start first became

NOTE Confidence: 0.931967356666666

00:03:29.279 --> 00:03:30.638 interested in neuroscience.

NOTE Confidence: 0.931967356666666

00:03:30.640 --> 00:03:32.716 It's this type of question that.

NOTE Confidence: 0.931967356666666

00:03:32.720 --> 00:03:34.068 Brought me to neuroscience,

NOTE Confidence: 0.931967356666666

00:03:34.068 --> 00:03:37.680 which this idea of how it is that the

NOTE Confidence: 0.931967356666666

00:03:37.680 --> 00:03:39.680 environment can sculpt developing circuits,

NOTE Confidence: 0.931967356666666

00:03:39.680 --> 00:03:39.988 right.

NOTE Confidence: 0.931967356666666

00:03:39.988 --> 00:03:42.144 So we know early in development with

NOTE Confidence: 0.931967356666666

00:03:42.144 --> 00:03:44.160 during this process of brain wiring,

NOTE Confidence: 0.931967356666666

00:03:44.160 --> 00:03:46.278 we start off with, you know,

NOTE Confidence: 0.931967356666666

00:03:46.280 --> 00:03:48.165 kind of a sparse immature

NOTE Confidence: 0.931967356666666

00:03:48.165 --> 00:03:48.919 synaptic connections.

NOTE Confidence: 0.931967356666666

00:03:48.920 --> 00:03:50.648 And then over a course of

NOTE Confidence: 0.931967356666666

00:03:50.648 --> 00:03:51.512 different critical periods,

NOTE Confidence: 0.931967356666666

00:03:51.520 --> 00:03:51.830 right,

NOTE Confidence: 0.931967356666666

00:03:51.830 --> 00:03:54.000 we start to develop this process by

NOTE Confidence: 0.931967356666666

00:03:54.000 --> 00:03:56.293 which some of those connections form

NOTE Confidence: 0.931967356666666

00:03:56.293 --> 00:03:58.308 and get strengthened and maintained.

NOTE Confidence: 0.931967356666666

00:03:58.310 --> 00:03:59.660 And other of these connections

NOTE Confidence: 0.931967356666666

00:03:59.660 --> 00:04:00.470 get permanently removed.

NOTE Confidence: 0.931967356666666

00:04:00.470 --> 00:04:02.678 This is a process called synaptic

NOTE Confidence: 0.931967356666666

00:04:02.678 --> 00:04:04.150 refinement or synaptic pruning,

NOTE Confidence: 0.931967356666666

00:04:04.150 --> 00:04:06.126 and we know what happens all across the

NOTE Confidence: 0.931967356666666

00:04:06.126 --> 00:04:08.270 brain in different critical periods now.

NOTE Confidence: 0.931967356666666

00:04:08.270 --> 00:04:09.866 It's been best studied in sensory

NOTE Confidence: 0.931967356666666

00:04:09.866 --> 00:04:11.813 systems like the visual system and for

NOTE Confidence: 0.931967356666666

00:04:11.813 --> 00:04:13.469 that matter many other sensory systems

NOTE Confidence: 0.931967356666666

00:04:13.469 --> 00:04:15.122 where these critical periods are

NOTE Confidence: 0.931967356666666

00:04:15.122 --> 00:04:16.782 often happening early in development,

NOTE Confidence: 0.931967356666666

00:04:16.790 --> 00:04:19.062 but other parts of your brain like the

NOTE Confidence: 0.931967356666666

00:04:19.062 --> 00:04:20.799 prefrontal cortex and cortical circuits.

NOTE Confidence: 0.931967356666666

00:04:20.800 --> 00:04:22.984 These are the sort of last areas

NOTE Confidence: 0.931967356666666

00:04:22.984 --> 00:04:25.386 to refine and mature and and

NOTE Confidence: 0.931967356666666

00:04:25.386 --> 00:04:26.372 incredibly important.

NOTE Confidence: 0.931967356666666

00:04:26.372 --> 00:04:27.358 You know,

NOTE Confidence: 0.931967356666666

00:04:27.360 --> 00:04:29.394 there's much less known about the

NOTE Confidence: 0.931967356666666

00:04:29.394 --> 00:04:31.520 mechanisms and and timelines that regulate

NOTE Confidence: 0.931967356666666

00:04:31.520 --> 00:04:34.160 those processes of synaptic refinement.

NOTE Confidence: 0.931967356666666

00:04:34.160 --> 00:04:36.022 So what we are interested in is

NOTE Confidence: 0.931967356666666

00:04:36.022 --> 00:04:37.882 trying to better define not only

NOTE Confidence: 0.931967356666666

00:04:37.882 --> 00:04:39.547 the timing of different regions

NOTE Confidence: 0.931967356666666

00:04:39.547 --> 00:04:41.440 and circuits and their maturation,

NOTE Confidence: 0.931967356666666

00:04:41.440 --> 00:04:43.610 but we want to try to better

NOTE Confidence: 0.931967356666666

00:04:43.610 --> 00:04:45.374 understand how perturbations of the

NOTE Confidence: 0.931967356666666

00:04:45.374 --> 00:04:46.926 environment and particular genetic

NOTE Confidence: 0.931967356666666

00:04:46.926 --> 00:04:48.775 pathways influence and change

NOTE Confidence: 0.931967356666666

00:04:48.775 --> 00:04:50.715 circuits and ultimately behavior.

NOTE Confidence: 0.931967356666666

00:04:50.720 --> 00:04:51.784 Now it's long known,

NOTE Confidence: 0.931967356666666

00:04:51.784 --> 00:04:52.316 you know,

NOTE Confidence: 0.931967356666666

00:04:52.320 --> 00:04:54.000 I should just mention another thing,

NOTE Confidence: 0.931967356666666

00:04:54.000 --> 00:04:55.320 that plasticity is usually thought

NOTE Confidence: 0.931967356666666

00:04:55.320 --> 00:04:56.640 to be a good thing.

NOTE Confidence: 0.931967356666666

00:04:56.640 --> 00:04:58.544 It's why my daughter can learn French

NOTE Confidence: 0.931967356666666

00:04:58.544 --> 00:05:00.519 seamlessly and I am terrible at French,

NOTE Confidence: 0.931967356666666

00:05:00.520 --> 00:05:00.842 right?

NOTE Confidence: 0.931967356666666

00:05:00.842 --> 00:05:03.096 My critical period for learning French is

NOTE Confidence: 0.931967356666666

00:05:03.096 --> 00:05:05.354 long closed and no matter how much I try,

NOTE Confidence: 0.931967356666666

00:05:05.360 --> 00:05:06.336 it is very challenging.

NOTE Confidence: 0.931967356666666

00:05:06.336 --> 00:05:08.131 But my both my daughters are in

NOTE Confidence: 0.931967356666666

00:05:08.131 --> 00:05:09.536 a French immersion program and

NOTE Confidence: 0.931967356666666

00:05:09.536 --> 00:05:11.044 started learning that when they

NOTE Confidence: 0.931967356666666

00:05:11.044 --> 00:05:12.356 were kindergarten first grade.

NOTE Confidence: 0.931967356666666

00:05:12.360 --> 00:05:14.040 And it's amazing, you know.

NOTE Confidence: 0.931967356666666

00:05:14.040 --> 00:05:16.024 So that's just one of one of many

NOTE Confidence: 0.931967356666666

00:05:16.024 --> 00:05:17.438 examples of why sort of this

NOTE Confidence: 0.931967356666666

00:05:17.438 --> 00:05:18.950 idea of lose it or use it.

NOTE Confidence: 0.931967356666666

00:05:18.950 --> 00:05:19.380 Lose it,

NOTE Confidence: 0.931967356666666

00:05:19.380 --> 00:05:21.100 use it or lose it and the idea

NOTE Confidence: 0.899246075

00:05:21.161 --> 00:05:22.816 that you know plasticity while

NOTE Confidence: 0.899246075

00:05:22.816 --> 00:05:24.471 enabling learning and and and

NOTE Confidence: 0.899246075

00:05:24.532 --> 00:05:26.188 adaptation to the environment,

NOTE Confidence: 0.899246075

00:05:26.190 --> 00:05:27.828 it can also lead to vulnerability.

NOTE Confidence: 0.899246075

00:05:27.830 --> 00:05:30.357 So plasticity opens the brain up for

NOTE Confidence: 0.899246075

00:05:30.357 --> 00:05:32.116 potential vulnerability because it's so

NOTE Confidence: 0.899246075

00:05:32.116 --> 00:05:34.272 dynamic and plastic and I think it's

NOTE Confidence: 0.899246075

00:05:34.272 --> 00:05:35.596 understanding these critical periods

NOTE Confidence: 0.899246075

00:05:35.596 --> 00:05:37.829 are going to be important to thinking

NOTE Confidence: 0.899246075

00:05:37.830 --> 00:05:40.212 about why there is particular windows

NOTE Confidence: 0.899246075

00:05:40.212 --> 00:05:42.313 of vulnerability and diseases and

NOTE Confidence: 0.899246075

00:05:42.313 --> 00:05:44.538 disorders like schizophrenia for example.

NOTE Confidence: 0.899246075

00:05:44.540 --> 00:05:46.252 Now schizophrenia, you know,

NOTE Confidence: 0.899246075

00:05:46.252 --> 00:05:48.216 we know is, you know,

NOTE Confidence: 0.899246075

00:05:48.216 --> 00:05:49.906 there's evidence from both imaging

NOTE Confidence: 0.899246075

00:05:49.906 --> 00:05:52.340 studies and some anatomical studies that

NOTE Confidence: 0.899246075

00:05:52.340 --> 00:05:55.220 there is a loss of great Gray matter,

NOTE Confidence: 0.899246075

00:05:55.220 --> 00:05:56.912 thinning of Gray matter and and

NOTE Confidence: 0.899246075

00:05:56.912 --> 00:05:58.710 even some evidence of loss of

NOTE Confidence: 0.899246075

00:05:58.710 --> 00:06:00.558 spines and synopses that have come

NOTE Confidence: 0.899246075

00:06:00.558 --> 00:06:01.660 from postmortem studies.

NOTE Confidence: 0.899246075

00:06:01.660 --> 00:06:03.683 And, and I think more and more

NOTE Confidence: 0.899246075

00:06:03.683 --> 00:06:05.632 evidence is suggesting that at least

NOTE Confidence: 0.899246075

00:06:05.632 --> 00:06:07.337 in some individuals of schizophrenia

NOTE Confidence: 0.899246075

00:06:07.340 --> 00:06:09.060 there's evidence of synaptic defects.

NOTE Confidence: 0.899246075

00:06:09.060 --> 00:06:10.660 And this is not true just of schizophrenia.

NOTE Confidence: 0.899246075

00:06:10.660 --> 00:06:12.765 This is true of other

NOTE Confidence: 0.899246075

00:06:12.765 --> 00:06:14.449 neurodevelopmental disorders as well.

NOTE Confidence: 0.899246075

00:06:14.450 --> 00:06:16.298 But I think the problem with

NOTE Confidence: 0.899246075

00:06:16.298 --> 00:06:17.530 these types of examples,

NOTE Confidence: 0.899246075

00:06:17.530 --> 00:06:18.397 even the imaging,

NOTE Confidence: 0.899246075

00:06:18.397 --> 00:06:20.786 it doesn't give you the resolution to look

NOTE Confidence: 0.899246075

00:06:20.786 --> 00:06:22.616 at synapses and the postmortem analysis

NOTE Confidence: 0.899246075

00:06:22.616 --> 00:06:25.169 where you can quantify synapses in patients.

NOTE Confidence: 0.899246075

00:06:25.170 --> 00:06:26.980 By the time you get those brains, you know

NOTE Confidence: 0.899246075

00:06:26.980 --> 00:06:28.210 there's many things that have happened.

NOTE Confidence: 0.899246075

00:06:28.210 --> 00:06:29.914 So you don't know whether that's

NOTE Confidence: 0.899246075

00:06:29.914 --> 00:06:30.990 cause or consequence, right.

NOTE Confidence: 0.899246075

00:06:30.990 --> 00:06:32.310 There are many things that could

NOTE Confidence: 0.899246075

00:06:32.310 --> 00:06:34.450 have led to the loss of synapses.

NOTE Confidence: 0.899246075

00:06:34.450 --> 00:06:36.730 So a lot of this idea of of

NOTE Confidence: 0.899246075

00:06:36.730 --> 00:06:37.890 synaptic pruning defects,

NOTE Confidence: 0.899246075

00:06:37.890 --> 00:06:39.927 those are all been, it's a hypothesis.

NOTE Confidence: 0.899246075

00:06:39.930 --> 00:06:42.150 We don't know for sure that

NOTE Confidence: 0.899246075

00:06:42.150 --> 00:06:44.050 synapse pruning or synapse loss.

NOTE Confidence: 0.899246075

00:06:44.050 --> 00:06:44.896 Is contributing to,

NOTE Confidence: 0.899246075

00:06:44.896 --> 00:06:45.178 to,

NOTE Confidence: 0.899246075

00:06:45.178 --> 00:06:47.244 to to some of these disorders and

NOTE Confidence: 0.899246075

00:06:47.244 --> 00:06:48.814 I think that's real obviously

NOTE Confidence: 0.899246075

00:06:48.814 --> 00:06:50.290 very challenging to study in,

NOTE Confidence: 0.899246075

00:06:50.290 --> 00:06:52.288 in people and for that matter

NOTE Confidence: 0.899246075

00:06:52.288 --> 00:06:53.287 even in animals.

NOTE Confidence: 0.899246075

00:06:53.290 --> 00:06:55.794 And so we also know that synapse loss

NOTE Confidence: 0.899246075

00:06:55.794 --> 00:06:57.804 and dysfunction is a is a hallmark

NOTE Confidence: 0.899246075

00:06:57.804 --> 00:06:59.490 of many other disorders as well.

NOTE Confidence: 0.899246075

00:06:59.490 --> 00:07:01.605 And my lab over the last many years has

NOTE Confidence: 0.899246075

00:07:01.605 --> 00:07:03.651 been studying normally what regulates

NOTE Confidence: 0.899246075

00:07:03.651 --> 00:07:05.846 synaptic pruning and synapse elimination,

NOTE Confidence: 0.899246075

00:07:05.850 --> 00:07:07.475 hoping that by understanding basic

NOTE Confidence: 0.899246075

00:07:07.475 --> 00:07:09.450 mechanisms in the normal healthy brain,

NOTE Confidence: 0.899246075

00:07:09.450 --> 00:07:11.285 in animal models and ideally

NOTE Confidence: 0.899246075

00:07:11.285 --> 00:07:12.386 in patient samples.

NOTE Confidence: 0.899246075

00:07:12.390 --> 00:07:14.040 That that can then based on

NOTE Confidence: 0.899246075

00:07:14.040 --> 00:07:14.865 that mechanistic understanding,

NOTE Confidence: 0.899246075

00:07:14.870 --> 00:07:16.935 we could then apply some of that

NOTE Confidence: 0.899246075

00:07:16.935 --> 00:07:18.680 to understand whether those same

NOTE Confidence: 0.899246075

00:07:18.680 --> 00:07:20.276 mechanisms become aberrantly activated

NOTE Confidence: 0.899246075

00:07:20.276 --> 00:07:22.239 to lead to pathological synapse

NOTE Confidence: 0.899246075

00:07:22.239 --> 00:07:24.069 loss in the context of disease.

NOTE Confidence: 0.899246075

00:07:24.070 --> 00:07:25.939 And we've also been studying this in

NOTE Confidence: 0.899246075

00:07:25.939 --> 00:07:27.122 other diseases including Alzheimer's

NOTE Confidence: 0.899246075

00:07:27.122 --> 00:07:28.121 and age-related neurodegenerative

NOTE Confidence: 0.899246075

00:07:28.121 --> 00:07:30.430 diseases and in fact in normal aging.

NOTE Confidence: 0.899246075

00:07:30.430 --> 00:07:32.397 And even though all of these disorders

NOTE Confidence: 0.899246075

00:07:32.397 --> 00:07:33.868 are remarkably different in many ways,

NOTE Confidence: 0.899246075

00:07:33.870 --> 00:07:34.938 as you all know,

NOTE Confidence: 0.899246075

00:07:34.938 --> 00:07:36.540 I believe there's still evidence of

NOTE Confidence: 0.899246075

00:07:36.596 --> 00:07:38.496 a convergence that I'm particularly

NOTE Confidence: 0.899246075

00:07:38.496 --> 00:07:40.016 interested in because different

NOTE Confidence: 0.899246075

00:07:40.016 --> 00:07:41.738 things can initiate the process.

NOTE Confidence: 0.899246075

00:07:41.740 --> 00:07:43.219 Genetics and environment,

NOTE Confidence: 0.899246075

00:07:43.219 --> 00:07:44.698 different different pathways,

NOTE Confidence: 0.899246075

00:07:44.700 --> 00:07:46.724 maybe even different circuits,

NOTE Confidence: 0.899246075

00:07:46.724 --> 00:07:48.985 but ultimately at least the data that

NOTE Confidence: 0.899246075

00:07:48.985 --> 00:07:50.230 we have suggests the possibility

NOTE Confidence: 0.899246075

00:07:50.284 --> 00:07:52.108 that there could be some converging

NOTE Confidence: 0.899246075

00:07:52.108 --> 00:07:53.324 mechanisms that then ultimately

NOTE Confidence: 0.899246075

00:07:53.373 --> 00:07:54.873 leads to the synaptic vulnerability

NOTE Confidence: 0.899246075

00:07:54.873 --> 00:07:55.773 and synapse loss.

NOTE Confidence: 0.899246075

00:07:55.780 --> 00:07:57.201 And that's what I want to talk

NOTE Confidence: 0.899246075

00:07:57.201 --> 00:07:58.140 to you about today.

NOTE Confidence: 0.899246075

00:07:58.140 --> 00:07:59.412 So why has progress been so

NOTE Confidence: 0.899246075

00:07:59.412 --> 00:08:00.260 slow on the biology

NOTE Confidence: 0.945524904761905

00:08:00.308 --> 00:08:01.880 side even though the genetics and

NOTE Confidence: 0.945524904761905

00:08:01.880 --> 00:08:03.380 the genomic studies have exploded?

NOTE Confidence: 0.945524904761905

00:08:03.380 --> 00:08:04.728 And that's wonderful because

NOTE Confidence: 0.945524904761905

00:08:04.728 --> 00:08:06.968 unbiased data is giving us, I know,

NOTE Confidence: 0.945524904761905

00:08:06.968 --> 00:08:08.612 new leads, new candidates and new

NOTE Confidence: 0.945524904761905

00:08:08.612 --> 00:08:10.618 ways of thinking about mechanism.

NOTE Confidence: 0.945524904761905

00:08:10.620 --> 00:08:12.500 But obviously this complex circuitry

NOTE Confidence: 0.945524904761905

00:08:12.500 --> 00:08:14.380 inaccessibility of the human brain,

NOTE Confidence: 0.945524904761905

00:08:14.380 --> 00:08:16.151 as I mentioned and as I'll highlight

NOTE Confidence: 0.945524904761905

00:08:16.151 --> 00:08:18.178 and I think many of you appreciate,

NOTE Confidence: 0.945524904761905

00:08:18.180 --> 00:08:19.710 there's been a lack of credible

NOTE Confidence: 0.945524904761905

00:08:19.710 --> 00:08:20.220 disease models.

NOTE Confidence: 0.945524904761905

00:08:20.220 --> 00:08:23.100 I mean, I don't think anyone model a mouse

NOTE Confidence: 0.945524904761905

00:08:23.100 --> 00:08:25.580 or monkey or other animal models can really,

NOTE Confidence: 0.945524904761905

00:08:25.580 --> 00:08:27.132 truly recapitulate the complexity

NOTE Confidence: 0.945524904761905

00:08:27.132 --> 00:08:29.460 of the human brain and cognition,

NOTE Confidence: 0.945524904761905

00:08:29.460 --> 00:08:31.469 but with the thoughtful way of thinking

NOTE Confidence: 0.945524904761905

00:08:31.469 --> 00:08:33.699 about trying to model disease mechanisms,

NOTE Confidence: 0.945524904761905

00:08:33.700 --> 00:08:35.000 not model the disease.

NOTE Confidence: 0.945524904761905

00:08:35.000 --> 00:08:36.300 That's giving us new,

NOTE Confidence: 0.945524904761905

00:08:36.300 --> 00:08:38.155 a new foothold into trying to understand

NOTE Confidence: 0.945524904761905

00:08:38.155 --> 00:08:40.300 the types of questions I raised before.

NOTE Confidence: 0.945524904761905

00:08:40.300 --> 00:08:42.058 And also we don't have biomarkers,

NOTE Confidence: 0.945524904761905

00:08:42.060 --> 00:08:42.431 right.

NOTE Confidence: 0.945524904761905

00:08:42.431 --> 00:08:45.028 We don't have really good mechanistic and

NOTE Confidence: 0.945524904761905

00:08:45.028 --> 00:08:46.939 predictive biomarkers given the complexity,

NOTE Confidence: 0.945524904761905

00:08:46.940 --> 00:08:48.440 heterogeneity and polygenicity

NOTE Confidence: 0.945524904761905

00:08:48.440 --> 00:08:49.940 of these disorders,

NOTE Confidence: 0.945524904761905

00:08:49.940 --> 00:08:52.070 how do you even know who to track and and

NOTE Confidence: 0.945524904761905

00:08:52.124 --> 00:08:54.098 follow and stratify and we don't have,

NOTE Confidence: 0.945524904761905

00:08:54.100 --> 00:08:56.700 we don't have that for for these disorders.

NOTE Confidence: 0.945524904761905

00:08:56.700 --> 00:08:58.142 So what I want to do today

NOTE Confidence: 0.945524904761905

00:08:58.142 --> 00:08:59.769 is kind of take you through.

NOTE Confidence: 0.945524904761905

00:08:59.770 --> 00:09:01.324 The thinking and the the way we've

NOTE Confidence: 0.945524904761905

00:09:01.324 --> 00:09:02.616 been thinking about how to tackle

NOTE Confidence: 0.945524904761905

00:09:02.616 --> 00:09:03.967 this and we meaning there's a lot

NOTE Confidence: 0.945524904761905

00:09:04.016 --> 00:09:05.004 of collaborators and colleagues

NOTE Confidence: 0.945524904761905

00:09:05.004 --> 00:09:06.803 at the Stanley Center at the broad

NOTE Confidence: 0.945524904761905

00:09:06.803 --> 00:09:08.368 and and within my lab.

NOTE Confidence: 0.945524904761905

00:09:08.370 --> 00:09:09.735 But just the idea that you know

NOTE Confidence: 0.945524904761905

00:09:09.735 --> 00:09:11.208 that there are many open questions.

NOTE Confidence: 0.945524904761905

00:09:11.210 --> 00:09:12.939 We still don't know even with all

NOTE Confidence: 0.945524904761905

00:09:12.939 --> 00:09:14.830 of the genetics that are pointing to

NOTE Confidence: 0.945524904761905

00:09:14.830 --> 00:09:16.468 variance that we don't many cases

NOTE Confidence: 0.945524904761905

00:09:16.519 --> 00:09:18.430 know what the genes are right they're

NOTE Confidence: 0.945524904761905

00:09:18.430 --> 00:09:20.135 they're close to in a particular

NOTE Confidence: 0.945524904761905

00:09:20.135 --> 00:09:21.905 chromosome and a particular loci but

NOTE Confidence: 0.945524904761905

00:09:21.905 --> 00:09:23.601 which genes in some cases we know

NOTE Confidence: 0.945524904761905

00:09:23.601 --> 00:09:25.567 the genes and in many cases we don't.

NOTE Confidence: 0.945524904761905

00:09:25.570 --> 00:09:27.355 We don't know the mechanism by which

NOTE Confidence: 0.945524904761905

00:09:27.355 --> 00:09:29.250 these genes actually alter cellular function.

NOTE Confidence: 0.945524904761905

00:09:29.250 --> 00:09:31.248 We don't know which pathways are

NOTE Confidence: 0.945524904761905

00:09:31.248 --> 00:09:32.994 relevant because these genes don't

NOTE Confidence: 0.945524904761905

00:09:32.994 --> 00:09:34.769 necessarily tell us what pathway.

NOTE Confidence: 0.945524904761905

00:09:34.770 --> 00:09:36.989 We don't know in many cases which

NOTE Confidence: 0.945524904761905

00:09:36.989 --> 00:09:39.087 cell types are are are most affected.

NOTE Confidence: 0.945524904761905

00:09:39.087 --> 00:09:40.749 There are loss of heterogeneity of

NOTE Confidence: 0.945524904761905

00:09:40.749 --> 00:09:42.809 cells in the brain, as you know,

NOTE Confidence: 0.945524904761905

00:09:42.809 --> 00:09:44.567 even with an excitatory neuron populations,

NOTE Confidence: 0.945524904761905

00:09:44.570 --> 00:09:46.265 inhibitory neuron populations,

NOTE Confidence: 0.945524904761905

00:09:46.265 --> 00:09:49.090 and glial cells remarkable heterogeneity.

NOTE Confidence: 0.945524904761905

00:09:49.090 --> 00:09:50.890 So even if you found a gene in a pathway,

NOTE Confidence: 0.945524904761905

00:09:50.890 --> 00:09:53.026 which cell type do you want to be

NOTE Confidence: 0.945524904761905

00:09:53.026 --> 00:09:54.436 studying right and what's which

NOTE Confidence: 0.945524904761905

00:09:54.436 --> 00:09:55.520 ones to focus on?

NOTE Confidence: 0.945524904761905

00:09:55.520 --> 00:09:57.040 And of course which synapse,

NOTE Confidence: 0.945524904761905

00:09:57.040 --> 00:09:58.280 right, it's not all synapses,

NOTE Confidence: 0.945524904761905

00:09:58.280 --> 00:09:59.468 maybe the vulnerable synapse,

NOTE Confidence: 0.945524904761905

00:09:59.468 --> 00:10:00.953 which circuit in the brain,

NOTE Confidence: 0.945524904761905

00:10:00.960 --> 00:10:02.200 I mean obviously this is going to sound

NOTE Confidence: 0.945524904761905

00:10:02.200 --> 00:10:03.357 like the most daunting thing ever,

NOTE Confidence: 0.945524904761905

00:10:03.360 --> 00:10:05.240 how we ever going to figure this out,

NOTE Confidence: 0.945524904761905

00:10:05.240 --> 00:10:07.508 but ultimately all of these questions

NOTE Confidence: 0.945524904761905

00:10:07.508 --> 00:10:10.490 are are are open in many ways and so.

NOTE Confidence: 0.945524904761905

00:10:10.490 --> 00:10:12.155 What we want to try to be able to

NOTE Confidence: 0.945524904761905

00:10:12.155 --> 00:10:14.347 do is think about ways to to step

NOTE Confidence: 0.945524904761905

00:10:14.347 --> 00:10:15.810 back and systematically go through.

NOTE Confidence: 0.945524904761905

00:10:15.810 --> 00:10:17.910 And in some cases where the leads

NOTE Confidence: 0.945524904761905

00:10:17.910 --> 00:10:18.810 are more reasonable,

NOTE Confidence: 0.945524904761905

00:10:18.810 --> 00:10:20.328 we know something about the biology.

NOTE Confidence: 0.945524904761905

00:10:20.330 --> 00:10:21.890 We're going deeper to try to

NOTE Confidence: 0.945524904761905

00:10:21.890 --> 00:10:22.410 understand mechanism.

NOTE Confidence: 0.945524904761905

00:10:22.410 --> 00:10:23.855 And in other cases we're

NOTE Confidence: 0.945524904761905

00:10:23.855 --> 00:10:25.300 letting the unbiased data come

NOTE Confidence: 0.9483042535

00:10:25.358 --> 00:10:27.284 in to nominate pathways and then

NOTE Confidence: 0.9483042535

00:10:27.284 --> 00:10:28.568 we're developing new models.

NOTE Confidence: 0.9483042535

00:10:28.570 --> 00:10:29.990 We wish to test that.

NOTE Confidence: 0.9483042535

00:10:29.990 --> 00:10:31.878 So I'm going to give you an example

NOTE Confidence: 0.9483042535

00:10:31.878 --> 00:10:33.854 in the first part of my talk that's

NOTE Confidence: 0.9483042535

00:10:33.854 --> 00:10:35.702 going to focus on one gene and

NOTE Confidence: 0.9483042535

00:10:35.702 --> 00:10:37.433 pathway and mechanism that we have

NOTE Confidence: 0.9483042535

00:10:37.433 --> 00:10:39.149 worked on for the last decade.

NOTE Confidence: 0.9483042535

00:10:39.150 --> 00:10:41.383 And it involves the complement cascade as

NOTE Confidence: 0.9483042535

00:10:41.383 --> 00:10:44.268 you heard a little bit in the introduction.

NOTE Confidence: 0.9483042535

00:10:44.270 --> 00:10:45.881 But I just want to tell you a little

NOTE Confidence: 0.9483042535

00:10:45.881 --> 00:10:47.266 bit about how this all started

NOTE Confidence: 0.9483042535

00:10:47.270 --> 00:10:49.166 because we knew from the genetics.

NOTE Confidence: 0.9483042535

00:10:49.170 --> 00:10:51.466 That by far the largest and most

NOTE Confidence: 0.9483042535

00:10:51.466 --> 00:10:53.362 mysterious genetic result has always been

NOTE Confidence: 0.9483042535

00:10:53.362 --> 00:10:55.570 this huge man in the Manhattan plot.

NOTE Confidence: 0.9483042535

00:10:55.570 --> 00:10:58.286 There's clear evidence of the MHC locust,

NOTE Confidence: 0.9483042535

00:10:58.290 --> 00:10:58.542 right?

NOTE Confidence: 0.9483042535

00:10:58.542 --> 00:11:00.306 This is the tallest peak in the

NOTE Confidence: 0.9483042535

00:11:00.306 --> 00:11:01.386 Manhattan plot, but yet,

NOTE Confidence: 0.9483042535

00:11:01.386 --> 00:11:02.826 and there's hundreds of genes

NOTE Confidence: 0.9483042535

00:11:02.826 --> 00:11:03.690 within that locust.

NOTE Confidence: 0.9483042535

00:11:03.690 --> 00:11:05.920 But it's been a mystery in terms of what gene

NOTE Confidence: 0.9483042535

00:11:05.974 --> 00:11:08.008 or genes underlie this incredible signal.

NOTE Confidence: 0.9483042535

00:11:08.010 --> 00:11:08.670 And even now,

NOTE Confidence: 0.9483042535

00:11:08.670 --> 00:11:10.210 with more and more genetics coming in,

NOTE Confidence: 0.9483042535

00:11:10.210 --> 00:11:12.289 that peak is still the highest peak.

NOTE Confidence: 0.9483042535

00:11:12.290 --> 00:11:14.170 And, and at the time,

NOTE Confidence: 0.9483042535

00:11:14.170 --> 00:11:15.605 I know geneticists were working on this.

NOTE Confidence: 0.9483042535

00:11:15.610 --> 00:11:17.224 And of course, more and more

NOTE Confidence: 0.9483042535

00:11:17.224 --> 00:11:19.090 data means more and more insight.

NOTE Confidence: 0.9483042535

00:11:19.090 --> 00:11:22.186 But it turns out that you know,

NOTE Confidence: 0.9483042535

00:11:22.186 --> 00:11:25.870 one of my very outstanding geneticists and

NOTE Confidence: 0.9483042535

00:11:25.870 --> 00:11:28.090 neurobiologists colleague Steve Mccarroll,

NOTE Confidence: 0.9483042535

00:11:28.090 --> 00:11:30.090 his lab was studying this locust more deeply,

NOTE Confidence: 0.9483042535

00:11:30.090 --> 00:11:31.764 was fine mapping and starting to

NOTE Confidence: 0.9483042535

00:11:31.764 --> 00:11:33.570 look into the locust to see what,

NOTE Confidence: 0.9483042535

00:11:33.570 --> 00:11:35.345 what's what could explain this

NOTE Confidence: 0.9483042535

00:11:35.345 --> 00:11:36.410 huge genetic signal.

NOTE Confidence: 0.9483042535

00:11:36.410 --> 00:11:37.058 And for many reasons,

NOTE Confidence: 0.9483042535

00:11:37.058 --> 00:11:38.410 and of course this work is published,

NOTE Confidence: 0.9483042535

00:11:38.410 --> 00:11:40.280 but I just want to take you through the main

NOTE Confidence: 0.9483042535

00:11:40.331 --> 00:11:42.203 findings that sets up the rest of the stock,

NOTE Confidence: 0.9483042535

00:11:42.210 --> 00:11:44.184 what he found and what Ashwin

NOTE Confidence: 0.9483042535

00:11:44.184 --> 00:11:45.830 Sekhart found in his lab.

NOTE Confidence: 0.9483042535

00:11:45.830 --> 00:11:48.230 Was that in within that locus

NOTE Confidence: 0.9483042535

00:11:48.230 --> 00:11:51.229 are is a gene complement C4.

NOTE Confidence: 0.9483042535

00:11:51.230 --> 00:11:54.038 Now C4 in humans there are

NOTE Confidence: 0.9483042535

00:11:54.038 --> 00:11:56.154 two isoforms of C422 genes,

NOTE Confidence: 0.9483042535

00:11:56.154 --> 00:11:58.910 C4 big A and C4 big B.

NOTE Confidence: 0.9483042535

00:11:58.910 --> 00:12:01.801 And it turns out when you looked at the

NOTE Confidence: 0.9483042535

00:12:01.801 --> 00:12:04.747 haplotype in terms of different individuals,

NOTE Confidence: 0.9483042535

00:12:04.750 --> 00:12:06.162 you can have different

NOTE Confidence: 0.9483042535

00:12:06.162 --> 00:12:07.767 combinations of C4A versus C4B.

NOTE Confidence: 0.9483042535

00:12:07.767 --> 00:12:10.040 So you can have multiple copies of a.

NOTE Confidence: 0.9483042535

00:12:10.040 --> 00:12:12.640 Multiple copies of B both and vice versa.

NOTE Confidence: 0.9483042535

00:12:12.640 --> 00:12:14.481 And what Steve and Ashwin managed to

NOTE Confidence: 0.9483042535

00:12:14.481 --> 00:12:16.486 do and they discovered that it's not

NOTE Confidence: 0.9483042535

00:12:16.486 --> 00:12:18.141 so much whether you have the gene or

NOTE Confidence: 0.9483042535

00:12:18.141 --> 00:12:19.520 not have the gene or whether there's

NOTE Confidence: 0.9483042535

00:12:19.520 --> 00:12:21.040 a loss of function of that gene.

NOTE Confidence: 0.9483042535

00:12:21.040 --> 00:12:23.452 How many copies of the particular

NOTE Confidence: 0.9483042535

00:12:23.452 --> 00:12:25.719 structural form of C4 is what,

NOTE Confidence: 0.9483042535

00:12:25.720 --> 00:12:27.320 what, what linked to risk.

NOTE Confidence: 0.9483042535

00:12:27.320 --> 00:12:29.480 And there's a really all of the data

NOTE Confidence: 0.9483042535

00:12:29.480 --> 00:12:31.158 was published number of years ago,

NOTE Confidence: 0.9483042535

00:12:31.160 --> 00:12:32.546 but I just want to highlight the

NOTE Confidence: 0.9483042535

00:12:32.546 --> 00:12:34.119 take home of this important study.

NOTE Confidence: 0.9483042535

00:12:34.120 --> 00:12:36.402 One is that they went to correlate

NOTE Confidence: 0.9483042535

00:12:36.402 --> 00:12:38.304 and they've mapped us back on

NOTE Confidence: 0.9483042535

00:12:38.304 --> 00:12:39.729 to the genetics and found.

NOTE Confidence: 0.9483042535

00:12:39.730 --> 00:12:41.476 Indeed it was the copy number

NOTE Confidence: 0.9483042535

00:12:41.476 --> 00:12:43.382 of C4A the conferred risk.

NOTE Confidence: 0.9483042535

00:12:43.382 --> 00:12:46.495 So the more copies of you of C4A1

NOTE Confidence: 0.9483042535

00:12:46.495 --> 00:12:48.275 individual had it significantly

NOTE Confidence: 0.9483042535

00:12:48.275 --> 00:12:49.610 increased schizophrenia risk.

NOTE Confidence: 0.9483042535

00:12:49.610 --> 00:12:51.080 But they also measured the

NOTE Confidence: 0.9483042535

00:12:51.080 --> 00:12:52.970 expression of C4 on the brain.

NOTE Confidence: 0.9483042535

00:12:52.970 --> 00:12:54.890 This was the other really important

NOTE Confidence: 0.9483042535

00:12:54.890 --> 00:12:56.062 finding C4 in complement is

NOTE Confidence: 0.9483042535

00:12:56.062 --> 00:12:57.127 expressed in the whole body.

NOTE Confidence: 0.9483042535

00:12:57.130 --> 00:12:58.546 But it was the brain expression

NOTE Confidence: 0.9483042535

00:12:58.546 --> 00:12:59.490 that correlated with all

NOTE Confidence: 0.9446563375

00:12:59.540 --> 00:13:00.630 this and when they measured

NOTE Confidence: 0.9446563375

00:13:00.630 --> 00:13:02.690 the RNA in the brain.

NOTE Confidence: 0.9446563375

00:13:02.690 --> 00:13:04.990 It was the higher expression

NOTE Confidence: 0.9446563375

00:13:04.990 --> 00:13:07.055 of C4 was also related to the

NOTE Confidence: 0.9446563375

00:13:07.055 --> 00:13:08.660 more copies of C4A you had.

NOTE Confidence: 0.9446563375

00:13:08.660 --> 00:13:10.751 So you're making more of the C4A

NOTE Confidence: 0.9446563375

00:13:10.751 --> 00:13:12.977 gene now around the time they

NOTE Confidence: 0.9446563375

00:13:12.980 --> 00:13:14.804 Steve and Ashwin and his lab

NOTE Confidence: 0.9446563375

00:13:14.804 --> 00:13:16.529 started to uncover this really

NOTE Confidence: 0.9446563375

00:13:16.529 --> 00:13:18.309 exciting and important finding.

NOTE Confidence: 0.9446563375

00:13:18.310 --> 00:13:19.950 Steve and I actually didn't realize that we,

NOTE Confidence: 0.9446563375

00:13:19.950 --> 00:13:21.070 our labs are right across

NOTE Confidence: 0.9446563375

00:13:21.070 --> 00:13:22.190 the street from each other.

NOTE Confidence: 0.9446563375

00:13:22.190 --> 00:13:24.278 And and so we started having

NOTE Confidence: 0.9446563375

00:13:24.278 --> 00:13:26.182 coffee and I started Ed Skulnik

NOTE Confidence: 0.9446563375

00:13:26.182 --> 00:13:27.360 and Steve ***** started inviting

NOTE Confidence: 0.9446563375

00:13:27.360 --> 00:13:28.590 me over to the Stanley Center.

NOTE Confidence: 0.9446563375

00:13:28.590 --> 00:13:30.190 I'm like, why they want to hang out with me?

NOTE Confidence: 0.9446563375

00:13:30.190 --> 00:13:31.877 Well, it turns out they wanted to

NOTE Confidence: 0.9446563375

00:13:31.877 --> 00:13:33.803 hang out with me because we were

NOTE Confidence: 0.9446563375

00:13:33.803 --> 00:13:35.525 studying this very same pathway since

NOTE Confidence: 0.9446563375

00:13:35.581 --> 00:13:37.429 I was a postdoc in Ben Barris's lab,

NOTE Confidence: 0.9446563375

00:13:37.430 --> 00:13:38.610 not thinking anything about

NOTE Confidence: 0.9446563375

00:13:38.610 --> 00:13:39.790 the genetics of schizophrenia.

NOTE Confidence: 0.9446563375

00:13:39.790 --> 00:13:41.596 But we were really going deep into

NOTE Confidence: 0.9446563375

00:13:41.596 --> 00:13:43.124 the biology of this complement

NOTE Confidence: 0.9446563375

00:13:43.124 --> 00:13:45.212 pathway in the context of synaptic

NOTE Confidence: 0.9446563375

00:13:45.212 --> 00:13:47.070 elimination and synaptic development.

NOTE Confidence: 0.9446563375

00:13:47.070 --> 00:13:48.230 So it's a great.

NOTE Confidence: 0.9446563375

00:13:48.230 --> 00:13:49.970 Adipitous example of how a biology

NOTE Confidence: 0.9446563375

00:13:50.027 --> 00:13:51.847 and genetics can come together

NOTE Confidence: 0.9446563375

00:13:51.847 --> 00:13:53.667 and lead to collaborative science

NOTE Confidence: 0.9446563375

00:13:53.723 --> 00:13:55.947 that can then enable one to try to

NOTE Confidence: 0.9446563375

00:13:55.947 --> 00:13:57.282 understand the biology underlying

NOTE Confidence: 0.9446563375

00:13:57.282 --> 00:13:58.826 those emerging genetic findings.

NOTE Confidence: 0.9446563375

00:13:58.830 --> 00:14:00.060 And I'm just going to highlight

NOTE Confidence: 0.9446563375

00:14:00.060 --> 00:14:01.561 some ongoing work and in no way have

NOTE Confidence: 0.9446563375

00:14:01.561 --> 00:14:02.710 we figured this out by the way,

NOTE Confidence: 0.9446563375

00:14:02.710 --> 00:14:04.780 but I'm going to tell you what we've learned.

NOTE Confidence: 0.9446563375

00:14:04.780 --> 00:14:06.476 I just want to tell you if those

NOTE Confidence: 0.9446563375

00:14:06.476 --> 00:14:08.099 that are already thinking about

NOTE Confidence: 0.9446563375

00:14:08.100 --> 00:14:09.290 when they learn about compliment

NOTE Confidence: 0.9446563375

00:14:09.290 --> 00:14:11.164 back in the day in Med school or

NOTE Confidence: 0.9446563375

00:14:11.164 --> 00:14:12.634 in grad school and your head is

NOTE Confidence: 0.9446563375

00:14:12.688 --> 00:14:14.416 starting to spin thinking about that,

NOTE Confidence: 0.9446563375

00:14:14.420 --> 00:14:14.996 don't worry,

NOTE Confidence: 0.9446563375

00:14:14.996 --> 00:14:17.300 I'm not going to make you relearn compliment.

NOTE Confidence: 0.9446563375

00:14:17.300 --> 00:14:19.076 The take home here is it's very complex

NOTE Confidence: 0.9446563375

00:14:19.076 --> 00:14:20.869 and even the immunologist yesterday I

NOTE Confidence: 0.9446563375

00:14:20.869 --> 00:14:22.813 was over in the Immunobiology department,

NOTE Confidence: 0.9446563375

00:14:22.820 --> 00:14:23.368 they said,

NOTE Confidence: 0.9446563375

00:14:23.368 --> 00:14:23.916 you know,

NOTE Confidence: 0.9446563375

00:14:23.916 --> 00:14:25.954 nobody really wants to talk about the

NOTE Confidence: 0.9446563375

00:14:25.954 --> 00:14:28.000 compliment cascade because it's so complex.

NOTE Confidence: 0.9446563375

00:14:28.000 --> 00:14:30.960 And and and in fact even like these

NOTE Confidence: 0.9446563375

00:14:30.960 --> 00:14:32.759 incredible immunologists try to avoid it.

NOTE Confidence: 0.9446563375

00:14:32.760 --> 00:14:34.352 So I I didn't feel so bad when

NOTE Confidence: 0.9446563375

00:14:34.352 --> 00:14:36.264 I when I didn't know much about

NOTE Confidence: 0.9446563375

00:14:36.264 --> 00:14:37.719 adaptive immunity or B cells.

NOTE Confidence: 0.9446563375

00:14:37.720 --> 00:14:39.580 But I do know something about

NOTE Confidence: 0.9446563375

00:14:39.580 --> 00:14:41.571 complement and that is these are

NOTE Confidence: 0.9446563375

00:14:41.571 --> 00:14:43.276 a group of complement secreted

NOTE Confidence: 0.9446563375

00:14:43.280 --> 00:14:45.195 proteins that exist throughout your

NOTE Confidence: 0.9446563375

00:14:45.195 --> 00:14:47.110 body and basically what complement

NOTE Confidence: 0.9446563375

00:14:47.170 --> 00:14:48.969 does is it helps it's our first

NOTE Confidence: 0.9446563375

00:14:48.969 --> 00:14:50.840 line of defense against a pathogen.

NOTE Confidence: 0.9446563375

00:14:50.840 --> 00:14:52.718 So think about a a pathogen,

NOTE Confidence: 0.9446563375

00:14:52.720 --> 00:14:53.893 a bacterial infection.

NOTE Confidence: 0.9446563375

00:14:53.893 --> 00:14:55.457 Before your slower adaptive

NOTE Confidence: 0.9446563375

00:14:55.457 --> 00:14:56.860 immune system kicks in,

NOTE Confidence: 0.9446563375

00:14:56.860 --> 00:14:59.152 the complement system kicks in really

NOTE Confidence: 0.9446563375

00:14:59.152 --> 00:15:01.940 fast and these start secreted and they,

NOTE Confidence: 0.9446563375

00:15:01.940 --> 00:15:02.772 if they're all there,

NOTE Confidence: 0.9446563375

00:15:02.772 --> 00:15:02.980 present,

NOTE Confidence: 0.9446563375

00:15:02.980 --> 00:15:04.096 whether that be in the periphery

NOTE Confidence: 0.9446563375

00:15:04.096 --> 00:15:05.380 and the blood or in the brain,

NOTE Confidence: 0.9446563375

00:15:05.380 --> 00:15:06.192 as I'll tell you.

NOTE Confidence: 0.9446563375

00:15:06.192 --> 00:15:07.705 That can then lead to a kind

NOTE Confidence: 0.9446563375

00:15:07.705 --> 00:15:08.657 of a domino effect,

NOTE Confidence: 0.9446563375

00:15:08.660 --> 00:15:10.355 a cascade that ultimately leads

NOTE Confidence: 0.9446563375

00:15:10.355 --> 00:15:12.769 to the tagging of some of those

NOTE Confidence: 0.9446563375

00:15:12.769 --> 00:15:14.399 complement components like C4 and

NOTE Confidence: 0.9446563375

00:15:14.399 --> 00:15:17.017 C3 on the surface of that pathogen.

NOTE Confidence: 0.9446563375

00:15:17.020 --> 00:15:19.102 And that brings in macrophages the

NOTE Confidence: 0.9446563375

00:15:19.102 --> 00:15:21.380 Pacman to then recognize and remove it.

NOTE Confidence: 0.9446563375

00:15:21.380 --> 00:15:22.785 And then that's a very

NOTE Confidence: 0.9446563375

00:15:22.785 --> 00:15:24.190 helpful process to get rid

NOTE Confidence: 0.942901794736842

00:15:24.250 --> 00:15:25.840 of infection or dead cells

NOTE Confidence: 0.942901794736842

00:15:25.840 --> 00:15:27.112 or debris very rapidly.

NOTE Confidence: 0.942901794736842

00:15:27.120 --> 00:15:29.037 Well, it turns out when I was a postdoc

NOTE Confidence: 0.942901794736842

00:15:29.037 --> 00:15:31.169 in Ben Barris's lab through an unbiased

NOTE Confidence: 0.942901794736842

00:15:31.169 --> 00:15:33.277 gene chip experiment way back in the day,

NOTE Confidence: 0.942901794736842

00:15:33.280 --> 00:15:35.085 we also uncovered an unexpected

NOTE Confidence: 0.942901794736842

00:15:35.085 --> 00:15:37.726 role for C1Q during this process of

NOTE Confidence: 0.942901794736842

00:15:37.726 --> 00:15:39.656 development and synapse pruning that

NOTE Confidence: 0.942901794736842

00:15:39.656 --> 00:15:42.239 we also were very surprised about.

NOTE Confidence: 0.942901794736842

00:15:42.240 --> 00:15:43.240 And what it turns out,

NOTE Confidence: 0.942901794736842

00:15:43.240 --> 00:15:45.100 I'm going to tell you about is the work we

NOTE Confidence: 0.942901794736842

00:15:45.147 --> 00:15:46.915 uncovered when I was still in Ben's lab.

NOTE Confidence: 0.942901794736842

00:15:46.920 --> 00:15:48.456 And this is a figure from

NOTE Confidence: 0.942901794736842

00:15:48.456 --> 00:15:49.480 that very first paper.

NOTE Confidence: 0.942901794736842

00:15:49.480 --> 00:15:51.004 What we realized is.

NOTE Confidence: 0.942901794736842

00:15:51.004 --> 00:15:51.766 And hypothesize,

NOTE Confidence: 0.942901794736842

00:15:51.770 --> 00:15:53.205 and this is really Ben and I

NOTE Confidence: 0.942901794736842

00:15:53.205 --> 00:15:54.075 brainstorming about what complement

NOTE Confidence: 0.942901794736842

00:15:54.075 --> 00:15:55.365 might be doing in the brain,

NOTE Confidence: 0.942901794736842

00:15:55.370 --> 00:15:56.850 the healthy brain, no infection,

NOTE Confidence: 0.942901794736842

00:15:56.850 --> 00:15:57.970 no disease, no challenge.

NOTE Confidence: 0.942901794736842

00:15:57.970 --> 00:15:59.090 But it turns out,

NOTE Confidence: 0.942901794736842

00:15:59.090 --> 00:16:00.650 just like the immune system,

NOTE Confidence: 0.942901794736842

00:16:00.650 --> 00:16:01.730 glial cells, neurons,

NOTE Confidence: 0.942901794736842

00:16:01.730 --> 00:16:03.530 they all express these complement

NOTE Confidence: 0.942901794736842

00:16:03.530 --> 00:16:04.769 components all the time.

NOTE Confidence: 0.942901794736842

00:16:04.770 --> 00:16:06.408 And they're present in the brain now.

NOTE Confidence: 0.942901794736842

00:16:06.410 --> 00:16:08.370 They're not always there at the same levels.

NOTE Confidence: 0.942901794736842

00:16:08.370 --> 00:16:09.790 In fact, during development,

NOTE Confidence: 0.942901794736842

00:16:09.790 --> 00:16:11.565 during critical periods of development,

NOTE Confidence: 0.942901794736842

00:16:11.570 --> 00:16:12.728 there's a lot more of it,

NOTE Confidence: 0.942901794736842

00:16:12.730 --> 00:16:14.848 not just present, but tagging synapses.

NOTE Confidence: 0.942901794736842

00:16:14.850 --> 00:16:17.328 So instead of tagging a bacterial cell,

NOTE Confidence: 0.942901794736842

00:16:17.330 --> 00:16:19.364 what we discovered was that these

NOTE Confidence: 0.942901794736842

00:16:19.364 --> 00:16:20.970 complement components can similarly tag.

NOTE Confidence: 0.942901794736842

00:16:20.970 --> 00:16:23.088 Leg of Synapse and that microglia,

NOTE Confidence: 0.942901794736842

00:16:23.090 --> 00:16:23.952 not macrophages,

NOTE Confidence: 0.942901794736842

00:16:23.952 --> 00:16:25.676 have expressed the receptors

NOTE Confidence: 0.942901794736842

00:16:25.676 --> 00:16:26.969 that recognize complement.

NOTE Confidence: 0.942901794736842

00:16:26.970 --> 00:16:28.095 And through that,

NOTE Confidence: 0.942901794736842

00:16:28.095 --> 00:16:29.970 that's one way that synapses,

NOTE Confidence: 0.942901794736842

00:16:29.970 --> 00:16:30.704 exuberant connections,

NOTE Confidence: 0.942901794736842

00:16:30.704 --> 00:16:32.906 axons and synapses then can get

NOTE Confidence: 0.942901794736842

00:16:32.906 --> 00:16:34.928 removed and engulfed by microglia.

NOTE Confidence: 0.942901794736842

00:16:34.930 --> 00:16:36.490 Now that was a hypothesis.

NOTE Confidence: 0.942901794736842

00:16:36.490 --> 00:16:37.890 Then over the last decade or more,

NOTE Confidence: 0.942901794736842

00:16:37.890 --> 00:16:39.605 my lab has gone on to test,

NOTE Confidence: 0.942901794736842

00:16:39.610 --> 00:16:42.050 but I I want to tell you 2 important points.

NOTE Confidence: 0.942901794736842

00:16:42.050 --> 00:16:44.726 One is that complement is there,

NOTE Confidence: 0.942901794736842

00:16:44.730 --> 00:16:46.566 you know, naturally in the brain,

NOTE Confidence: 0.942901794736842

00:16:46.570 --> 00:16:48.018 right under normal conditions.

NOTE Confidence: 0.942901794736842

00:16:48.018 --> 00:16:50.190 It tags subsets of immature synapses

NOTE Confidence: 0.942901794736842

00:16:50.246 --> 00:16:51.786 during critical periods and we

NOTE Confidence: 0.942901794736842

00:16:51.786 --> 00:16:53.760 studied this in the visual system.

NOTE Confidence: 0.942901794736842

00:16:53.760 --> 00:16:55.615 We also went on to show if

NOTE Confidence: 0.942901794736842

00:16:55.615 --> 00:16:56.640 you genetically knock out

NOTE Confidence: 0.941437529411765

00:16:59.320 --> 00:17:00.490 C1QC3CR3 on the microglia through

NOTE Confidence: 0.941437529411765

00:17:00.490 --> 00:17:01.885 a number of studies over the

NOTE Confidence: 0.941437529411765

00:17:01.885 --> 00:17:02.959 years by my lab and others,

NOTE Confidence: 0.941437529411765

00:17:02.960 --> 00:17:06.124 that does lead to defects in synapse

NOTE Confidence: 0.941437529411765

00:17:06.124 --> 00:17:07.780 number and synaptic connectivity.

NOTE Confidence: 0.941437529411765

00:17:07.780 --> 00:17:09.580 We really focused on the visual

NOTE Confidence: 0.941437529411765

00:17:09.580 --> 00:17:11.565 system and we've gone deep into the

NOTE Confidence: 0.941437529411765

00:17:11.565 --> 00:17:13.107 visual system because it's such an

NOTE Confidence: 0.941437529411765

00:17:13.156 --> 00:17:14.997 elegant model to study the process of.

NOTE Confidence: 0.941437529411765

00:17:15.000 --> 00:17:16.245 Synaptic elimination and I'm going

NOTE Confidence: 0.941437529411765

00:17:16.245 --> 00:17:17.959 to take you through some of those

NOTE Confidence: 0.941437529411765

00:17:17.959 --> 00:17:19.436 mechanisms now and I'm going to come

NOTE Confidence: 0.941437529411765

00:17:19.436 --> 00:17:21.079 back out again and tell you how that

NOTE Confidence: 0.941437529411765

00:17:21.079 --> 00:17:23.068 might then lead to us thinking about

NOTE Confidence: 0.941437529411765

00:17:23.068 --> 00:17:25.150 synapse and vulnerability in the context

NOTE Confidence: 0.941437529411765

00:17:25.208 --> 00:17:27.198 of of disorders like schizophrenia.

NOTE Confidence: 0.941437529411765

00:17:27.200 --> 00:17:29.504 So the question we had in early on

NOTE Confidence: 0.941437529411765

00:17:29.504 --> 00:17:31.321 was could microglia be similarly

NOTE Confidence: 0.941437529411765

00:17:31.321 --> 00:17:33.673 playing this role in the brain?

NOTE Confidence: 0.941437529411765

00:17:33.680 --> 00:17:35.000 And as you just heard,

NOTE Confidence: 0.941437529411765

00:17:35.000 --> 00:17:36.600 you know, back then again,

NOTE Confidence: 0.941437529411765

00:17:36.600 --> 00:17:37.760 while a long time ago,

NOTE Confidence: 0.941437529411765

00:17:37.760 --> 00:17:38.711 15 years ago,

NOTE Confidence: 0.941437529411765

00:17:38.711 --> 00:17:40.930 microglia were really studied in the context

NOTE Confidence: 0.941437529411765

00:17:40.987 --> 00:17:43.115 of injury and disease or infection and,

NOTE Confidence: 0.941437529411765

00:17:43.120 --> 00:17:44.478 you know, other challenges in the brain.

NOTE Confidence: 0.941437529411765

00:17:44.480 --> 00:17:46.440 So we knew microglia are really important.

NOTE Confidence: 0.941437529411765

00:17:46.440 --> 00:17:48.265 But this observation made initially

NOTE Confidence: 0.941437529411765

00:17:48.265 --> 00:17:50.500 by my colleague at Stanford and

NOTE Confidence: 0.941437529411765

00:17:50.500 --> 00:17:52.240 others using two photon imaging,

NOTE Confidence: 0.941437529411765

00:17:52.240 --> 00:17:54.417 this is a movie by my own

NOTE Confidence: 0.941437529411765

00:17:54.417 --> 00:17:55.920 graduate student Janelle Wallace,

NOTE Confidence: 0.941437529411765

00:17:55.920 --> 00:17:56.820 just shows this.

NOTE Confidence: 0.941437529411765

00:17:56.820 --> 00:17:58.020 Really important observation that

NOTE Confidence: 0.941437529411765

00:17:58.020 --> 00:17:59.866 if you were to put a microscope

NOTE Confidence: 0.941437529411765

00:17:59.866 --> 00:18:01.500 in your head right now and watch

NOTE Confidence: 0.941437529411765

00:18:01.500 --> 00:18:03.236 microglia as you listen to my talk,

NOTE Confidence: 0.941437529411765

00:18:03.240 --> 00:18:05.277 they might be doing something like this.

NOTE Confidence: 0.941437529411765

00:18:05.280 --> 00:18:06.920 They're always moving their processes,

NOTE Confidence: 0.941437529411765

00:18:06.920 --> 00:18:07.742 they're moving around,

NOTE Confidence: 0.941437529411765

00:18:07.742 --> 00:18:09.112 they're touching synopses and a

NOTE Confidence: 0.941437529411765

00:18:09.112 --> 00:18:10.839 lot of other cells in the brain.

NOTE Confidence: 0.941437529411765

00:18:10.840 --> 00:18:12.268 This is just a sparse example

NOTE Confidence: 0.941437529411765

00:18:12.268 --> 00:18:14.092 where you can see the interactions

NOTE Confidence: 0.941437529411765

00:18:14.092 --> 00:18:15.716 between synopses and microglia.

NOTE Confidence: 0.941437529411765

00:18:15.720 --> 00:18:17.720 But this led to all kinds of just

NOTE Confidence: 0.941437529411765

00:18:17.720 --> 00:18:19.299 this observation alone led me to

NOTE Confidence: 0.941437529411765

00:18:19.299 --> 00:18:20.579 wonder all kinds of questions.

NOTE Confidence: 0.941437529411765

00:18:20.580 --> 00:18:21.645 What are they sensing when

NOTE Confidence: 0.941437529411765

00:18:21.645 --> 00:18:22.497 they're touching a synapse?

NOTE Confidence: 0.941437529411765

00:18:22.500 --> 00:18:23.660 What are the molecular cues

NOTE Confidence: 0.941437529411765

00:18:23.660 --> 00:18:24.820 that might be recruiting them?

NOTE Confidence: 0.941437529411765

00:18:24.820 --> 00:18:26.590 Find me signals to bring them

NOTE Confidence: 0.941437529411765

00:18:26.590 --> 00:18:28.220 in when they get there,

NOTE Confidence: 0.941437529411765

00:18:28.220 --> 00:18:29.557 some of them land and hang out

NOTE Confidence: 0.941437529411765

00:18:29.557 --> 00:18:30.620 with synapses longer than others,

NOTE Confidence: 0.941437529411765

00:18:30.620 --> 00:18:31.848 and others pull back.

NOTE Confidence: 0.941437529411765

00:18:31.848 --> 00:18:33.690 What are those molecules and what

NOTE Confidence: 0.941437529411765

00:18:33.747 --> 00:18:36.123 are the the sort of bidirectional

NOTE Confidence: 0.941437529411765

00:18:36.123 --> 00:18:37.707 signaling mechanisms between microgly

NOTE Confidence: 0.941437529411765

00:18:37.768 --> 00:18:39.710 and neurons that could be, you know,

NOTE Confidence: 0.941437529411765

00:18:39.710 --> 00:18:41.180 leading to this sort of interaction?

NOTE Confidence: 0.941437529411765

00:18:41.180 --> 00:18:42.224 But most importantly.

NOTE Confidence: 0.941437529411765

00:18:42.224 --> 00:18:43.860 You know, what's the functional consequence?

NOTE Confidence: 0.941437529411765

00:18:43.860 --> 00:18:45.035 What might they be doing?

NOTE Confidence: 0.941437529411765

00:18:45.040 --> 00:18:46.600 And as a resident phagocyte,

NOTE Confidence: 0.941437529411765

00:18:46.600 --> 00:18:47.656 and based on the mechanisms I

NOTE Confidence: 0.941437529411765

00:18:47.656 --> 00:18:48.800 told you about with complement,

NOTE Confidence: 0.941437529411765

00:18:48.800 --> 00:18:51.374 we hypothesize that maybe subsets of

NOTE Confidence: 0.941437529411765

00:18:51.374 --> 00:18:53.090 those synapses during development

NOTE Confidence: 0.941437529411765

00:18:53.157 --> 00:18:55.253 might actually be engulfed or phagocyte

NOTE Confidence: 0.941437529411765

00:18:55.253 --> 00:18:57.359 toast or pruned away by microglia.

NOTE Confidence: 0.941437529411765

00:18:57.360 --> 00:18:59.160 The weaker synapse is what we

NOTE Confidence: 0.941437529411765

00:18:59.160 --> 00:19:00.735 hypothesize and indeed in the

NOTE Confidence: 0.941437529411765

00:19:00.735 --> 00:19:02.315 visual system and the retina

NOTE Confidence: 0.941437529411765

00:19:02.315 --> 00:19:03.970 geniculate system that we study.

NOTE Confidence: 0.941437529411765

00:19:03.970 --> 00:19:05.698 We have a way thanks to the work

NOTE Confidence: 0.941437529411765

00:19:05.698 --> 00:19:07.304 of Carla Schatz and Shinfei Chen

NOTE Confidence: 0.941437529411765

00:19:07.304 --> 00:19:09.324 and and many others that have used

NOTE Confidence: 0.941437529411765

00:19:09.324 --> 00:19:11.319 so Huebel and weasel the system to

NOTE Confidence: 0.941437529411765

00:19:11.319 --> 00:19:12.678 study activity dependent refinement.

NOTE Confidence: 0.941437529411765

00:19:12.678 --> 00:19:15.830 You can basically in a mouse or a

NOTE Confidence: 0.941437529411765

00:19:15.903 --> 00:19:18.106 cat or a monkey, but we do mice.

NOTE Confidence: 0.941437529411765

00:19:18.106 --> 00:19:20.889 You can put tracers in the eyes of both mice,

NOTE Confidence: 0.941437529411765

00:19:20.890 --> 00:19:23.650 both eyes of of a mouse in red and and blue,

NOTE Confidence: 0.941437529411765

00:19:23.650 --> 00:19:25.302 and then that it leads to the

NOTE Confidence: 0.941437529411765

00:19:25.302 --> 00:19:26.010 tracing of the

NOTE Confidence: 0.933551393333333

00:19:26.072 --> 00:19:28.007 projection into the visual thalamus.

NOTE Confidence: 0.933551393333333

00:19:28.010 --> 00:19:29.809 And a cartoon of the relay neuron

NOTE Confidence: 0.933551393333333

00:19:29.809 --> 00:19:31.737 on the thalamus might look something

NOTE Confidence: 0.933551393333333

00:19:31.737 --> 00:19:33.205 like this early development.

NOTE Confidence: 0.933551393333333

00:19:33.210 --> 00:19:35.238 There's a neurons innervated by both

NOTE Confidence: 0.933551393333333

00:19:35.238 --> 00:19:37.329 eyes and they're pretty weak inputs.

NOTE Confidence: 0.933551393333333

00:19:37.330 --> 00:19:38.640 But during the critical period

NOTE Confidence: 0.933551393333333

00:19:38.640 --> 00:19:39.688 in Post Natal development,

NOTE Confidence: 0.933551393333333

00:19:39.690 --> 00:19:40.762 some of those inputs,

NOTE Confidence: 0.933551393333333

00:19:40.762 --> 00:19:43.161 the weak ones get pruned away and weakened

NOTE Confidence: 0.933551393333333

00:19:43.161 --> 00:19:45.369 and others get strengthened and maintained.

NOTE Confidence: 0.933551393333333

00:19:45.370 --> 00:19:46.882 This is the idea of use it or lose

NOTE Confidence: 0.933551393333333

00:19:46.882 --> 00:19:48.369 it and it's activity dependent.

NOTE Confidence: 0.933551393333333

00:19:48.370 --> 00:19:49.528 So based on all that work,

NOTE Confidence: 0.933551393333333

00:19:49.530 --> 00:19:52.356 we wondered a a micro engulfing

NOTE Confidence: 0.933551393333333

00:19:52.356 --> 00:19:54.849 or pruning synapses and if so,

NOTE Confidence: 0.933551393333333

00:19:54.850 --> 00:19:56.370 are they doing it in a selective way,

NOTE Confidence: 0.933551393333333

00:19:56.370 --> 00:19:57.794 is it activity dependent?

NOTE Confidence: 0.933551393333333

00:19:57.794 --> 00:19:59.574 The alternative less interesting hypothesis

NOTE Confidence: 0.933551393333333

00:19:59.574 --> 00:20:01.769 is they're just cleaning up the debris.

NOTE Confidence: 0.933551393333333

00:20:01.770 --> 00:20:03.490 And a lot of data supports that's that.

NOTE Confidence: 0.933551393333333

00:20:03.490 --> 00:20:04.862 It's the first that they're not just

NOTE Confidence: 0.933551393333333

00:20:04.862 --> 00:20:06.329 cleaning up and picking up the debris,

NOTE Confidence: 0.933551393333333

00:20:06.330 --> 00:20:07.746 but they're having a more active

NOTE Confidence: 0.933551393333333

00:20:07.746 --> 00:20:08.690 role in this process.

NOTE Confidence: 0.933551393333333

00:20:08.690 --> 00:20:10.412 Because work by Dorothy Schaefer in

NOTE Confidence: 0.933551393333333

00:20:10.412 --> 00:20:12.622 my lab showed that when you manipulate

NOTE Confidence: 0.933551393333333

00:20:12.622 --> 00:20:14.967 activity in the two eyes drive competition,

NOTE Confidence: 0.933551393333333

00:20:14.970 --> 00:20:17.185 there was a selective elimination

NOTE Confidence: 0.933551393333333

00:20:17.185 --> 00:20:19.400 or removal or phagocytosis of

NOTE Confidence: 0.933551393333333

00:20:19.471 --> 00:20:21.367 those presynaptic axons in,

NOTE Confidence: 0.933551393333333

00:20:21.370 --> 00:20:22.987 in a way that they were selectively

NOTE Confidence: 0.933551393333333

00:20:22.987 --> 00:20:24.290 engulfing the less active input.

NOTE Confidence: 0.933551393333333

00:20:24.290 --> 00:20:26.458 So this is an important sort of early

NOTE Confidence: 0.933551393333333

00:20:26.458 --> 00:20:27.817 finding because it did tell us.

NOTE Confidence: 0.933551393333333

00:20:27.820 --> 00:20:29.084 That it's, you know,

NOTE Confidence: 0.933551393333333

00:20:29.084 --> 00:20:30.664 instructive cues must somehow be

NOTE Confidence: 0.933551393333333

00:20:30.664 --> 00:20:32.397 regulating this process so that the

NOTE Confidence: 0.933551393333333

00:20:32.397 --> 00:20:34.085 less active inputs perhaps may have

NOTE Confidence: 0.933551393333333

00:20:34.085 --> 00:20:35.470 molecular cues that are different

NOTE Confidence: 0.933551393333333

00:20:35.470 --> 00:20:37.399 than the than the red inputs and

NOTE Confidence: 0.933551393333333

00:20:37.399 --> 00:20:39.310 then that might lead to microglia to

NOTE Confidence: 0.933551393333333

00:20:39.369 --> 00:20:41.295 then come and engulf those synapses.

NOTE Confidence: 0.933551393333333

00:20:41.300 --> 00:20:42.596 And we have a quite a bit of data

NOTE Confidence: 0.933551393333333

00:20:42.596 --> 00:20:43.740 to support that hypothesis,

NOTE Confidence: 0.933551393333333

00:20:43.740 --> 00:20:45.616 at least in the mouse visual system.

NOTE Confidence: 0.933551393333333

00:20:45.620 --> 00:20:47.764 So how does this relate to the complement

NOTE Confidence: 0.933551393333333

00:20:47.764 --> 00:20:49.586 C4 story I told you in genetics?

NOTE Confidence: 0.933551393333333

00:20:49.590 --> 00:20:49.865 Well,

NOTE Confidence: 0.933551393333333

00:20:49.865 --> 00:20:51.240 we started collaborating with Steve

NOTE Confidence: 0.933551393333333

00:20:51.240 --> 00:20:52.340 Mccarroll and we collaborated

NOTE Confidence: 0.933551393333333

00:20:52.386 --> 00:20:53.586 with also with an immunologist,

NOTE Confidence: 0.933551393333333

00:20:53.590 --> 00:20:56.110 a wonderful immunologist at Harvard,

NOTE Confidence: 0.933551393333333

00:20:56.110 --> 00:20:56.884 Michael Carroll,

NOTE Confidence: 0.933551393333333

00:20:56.884 --> 00:20:59.206 who actually cloned C4 and have

NOTE Confidence: 0.933551393333333

00:20:59.206 --> 00:21:01.426 been studying C4 in the context of

NOTE Confidence: 0.933551393333333

00:21:01.426 --> 00:21:03.185 lupus and in many other contexts

NOTE Confidence: 0.933551393333333

00:21:03.185 --> 00:21:05.105 in the immune system and using

NOTE Confidence: 0.933551393333333

00:21:05.105 --> 00:21:07.230 a combination of of mouse models

NOTE Confidence: 0.933551393333333

00:21:07.230 --> 00:21:08.670 that Mike's lab generated,

NOTE Confidence: 0.933551393333333

00:21:08.670 --> 00:21:10.536 C4 knockouts and other model I'll

NOTE Confidence: 0.933551393333333

00:21:10.536 --> 00:21:13.043 tell you about in a moment and a

NOTE Confidence: 0.933551393333333

00:21:13.043 --> 00:21:14.837 human IPS neurons and human tissue

NOTE Confidence: 0.933551393333333

00:21:14.902 --> 00:21:16.778 we showed that much like C1Q and

NOTE Confidence: 0.933551393333333

00:21:16.778 --> 00:21:19.794 C3 we could also see C4 decorating.

NOTE Confidence: 0.933551393333333

00:21:19.794 --> 00:21:22.549 Operating synopses in in neurons.

NOTE Confidence: 0.933551393333333

00:21:22.550 --> 00:21:24.545 And we also using the same kind

NOTE Confidence: 0.933551393333333

00:21:24.545 --> 00:21:26.614 of model system that I told you

NOTE Confidence: 0.933551393333333

00:21:26.614 --> 00:21:28.330 about earlier when we looked at

NOTE Confidence: 0.933551393333333

00:21:28.391 --> 00:21:29.789 pruning and refinement.

NOTE Confidence: 0.933551393333333

00:21:29.790 --> 00:21:33.306 C4 knockout mice Pheno copy the

NOTE Confidence: 0.933551393333333

00:21:33.310 --> 00:21:35.488 C1QC3CR3 mice again suggesting that the

NOTE Confidence: 0.933551393333333

00:21:35.488 --> 00:21:38.297 C4 similarly at least in a mouse was

NOTE Confidence: 0.933551393333333

00:21:38.297 --> 00:21:40.229 was was mediating the synaptic pruning.

NOTE Confidence: 0.933551393333333

00:21:40.230 --> 00:21:41.714 That's a loss of function but that's

NOTE Confidence: 0.933551393333333

00:21:41.714 --> 00:21:43.390 not what the genetics is telling us.

NOTE Confidence: 0.933551393333333

00:21:43.390 --> 00:21:45.460 Remember it's telling us too

NOTE Confidence: 0.933551393333333

00:21:45.460 --> 00:21:47.530 much C4 too much complement.

NOTE Confidence: 0.933551393333333

00:21:47.530 --> 00:21:49.154 And so too much C4 could mean

NOTE Confidence: 0.933551393333333

00:21:49.154 --> 00:21:50.370 more tagging of synapses,

NOTE Confidence: 0.933551393333333

00:21:50.370 --> 00:21:52.098 but it could also mean more

NOTE Confidence: 0.933551393333333

00:21:52.098 --> 00:21:53.587 activation of the classical comp

NOTE Confidence: 0.933551393333333

00:21:53.587 --> 00:21:55.279 and cascade because C4 is necessary

NOTE Confidence: 0.933551393333333

00:21:55.279 --> 00:21:57.129 for the whole pathway to happen.

NOTE Confidence: 0.933551393333333

00:21:57.130 --> 00:21:59.162 So the question was?

NOTE Confidence: 0.933551393333333

00:21:59.162 --> 00:22:00.686 Increase C4 levels,

NOTE Confidence: 0.844605326

00:22:00.690 --> 00:22:02.290 it lead to excessive burning.

NOTE Confidence: 0.844605326

00:22:02.290 --> 00:22:03.646 So this is more recent work.

NOTE Confidence: 0.844605326

00:22:03.650 --> 00:22:06.402 And so this necessitated the need to develop

NOTE Confidence: 0.844605326

00:22:06.402 --> 00:22:08.655 new models and in particular humanized

NOTE Confidence: 0.844605326

00:22:08.655 --> 00:22:11.410 mouse models that we didn't have before.

NOTE Confidence: 0.844605326

00:22:11.410 --> 00:22:13.650 And so Mike Carroll's lab developed a

NOTE Confidence: 0.844605326

00:22:13.650 --> 00:22:16.541 C4A humanized mouse model when he could

NOTE Confidence: 0.844605326

00:22:16.541 --> 00:22:18.698 introduce human C4A alleles into the

NOTE Confidence: 0.844605326

00:22:18.698 --> 00:22:20.690 mouse genome using back DNA transgenesis.

NOTE Confidence: 0.844605326

00:22:20.690 --> 00:22:23.055 So you can basically introduce

NOTE Confidence: 0.844605326

00:22:23.055 --> 00:22:24.646 human C4A or B in this case.

NOTE Confidence: 0.844605326

00:22:24.650 --> 00:22:26.246 I'm just telling you about a.

NOTE Confidence: 0.844605326

00:22:26.250 --> 00:22:29.346 Based on the you put it in AC4 knockout

NOTE Confidence: 0.844605326

00:22:29.346 --> 00:22:31.322 background and based on the the crosses

NOTE Confidence: 0.844605326

00:22:31.322 --> 00:22:33.569 that you do hets versus homozygous,

NOTE Confidence: 0.844605326

00:22:33.570 --> 00:22:35.250 you can also control copy number.

NOTE Confidence: 0.844605326

00:22:35.250 --> 00:22:36.414 So it's pretty cool.

NOTE Confidence: 0.844605326

00:22:36.414 --> 00:22:39.373 So as a proof of concept we wanted to know

NOTE Confidence: 0.844605326

00:22:39.373 --> 00:22:42.370 by making a mouse that has a lot of the

NOTE Confidence: 0.844605326

00:22:42.370 --> 00:22:44.694 genetic risk variant C4A over express.

NOTE Confidence: 0.844605326

00:22:44.694 --> 00:22:45.630 Versus C4B,

NOTE Confidence: 0.844605326

00:22:45.630 --> 00:22:46.910 which I'm not showing you.

NOTE Confidence: 0.844605326

00:22:46.910 --> 00:22:49.171 Does that in fact lead to using

NOTE Confidence: 0.844605326

00:22:49.171 --> 00:22:51.201 similar assays over pruning more

NOTE Confidence: 0.844605326

00:22:51.201 --> 00:22:53.185 microgly engulfment less synapses?

NOTE Confidence: 0.844605326

00:22:53.190 --> 00:22:55.496 And in the first study that was

NOTE Confidence: 0.844605326

00:22:55.496 --> 00:22:57.014 led by Mike Carroll's lab in

NOTE Confidence: 0.844605326

00:22:57.014 --> 00:22:58.486 collaboration with all of us showed

NOTE Confidence: 0.844605326

00:22:58.486 --> 00:22:59.866 using many of the same mechanisms,

NOTE Confidence: 0.844605326

00:22:59.870 --> 00:23:02.030 I just told you in the assays that

NOTE Confidence: 0.844605326

00:23:02.030 --> 00:23:04.171 indeed in the visual system and in

NOTE Confidence: 0.844605326

00:23:04.171 --> 00:23:06.993 the in the frontal cortex and in other

NOTE Confidence: 0.844605326

00:23:06.993 --> 00:23:09.028 regions they showed enhanced engulfment.

NOTE Confidence: 0.844605326

00:23:09.030 --> 00:23:09.704 And also,

NOTE Confidence: 0.844605326

00:23:09.704 --> 00:23:12.870 they also went on to show a spine loss,

NOTE Confidence: 0.844605326

00:23:12.870 --> 00:23:13.108 which,

NOTE Confidence: 0.844605326

00:23:13.108 --> 00:23:13.584 you know,

NOTE Confidence: 0.844605326

00:23:13.584 --> 00:23:14.774 this was really interesting because

NOTE Confidence: 0.844605326

00:23:14.774 --> 00:23:16.376 a lot of the work we had done

NOTE Confidence: 0.844605326

00:23:16.376 --> 00:23:17.746 in the visual system was a bit

NOTE Confidence: 0.844605326

00:23:17.746 --> 00:23:18.746 more on the presynaptic side.

NOTE Confidence: 0.844605326

00:23:18.750 --> 00:23:20.230 So this is now looking in the cortex,

NOTE Confidence: 0.844605326

00:23:20.230 --> 00:23:21.258 getting closer to where

NOTE Confidence: 0.844605326

00:23:21.258 --> 00:23:22.543 I was wanting to head,

NOTE Confidence: 0.844605326

00:23:22.550 --> 00:23:23.850 but we weren't quite brave

NOTE Confidence: 0.844605326

00:23:23.850 --> 00:23:25.150 enough to go there yet.

NOTE Confidence: 0.844605326

00:23:25.150 --> 00:23:26.865 So what is all this telling us?

NOTE Confidence: 0.844605326

00:23:26.870 --> 00:23:28.148 And there's a lot more I'm not telling you.

NOTE Confidence: 0.844605326

00:23:28.150 --> 00:23:30.982 This paper was just published in 2020 if

NOTE Confidence: 0.844605326

00:23:30.982 --> 00:23:33.510 you want to learn more about this study.

NOTE Confidence: 0.844605326

00:23:33.510 --> 00:23:35.710 But the working model,

NOTE Confidence: 0.844605326

00:23:35.710 --> 00:23:37.558 and this is building on a lot

NOTE Confidence: 0.844605326

00:23:37.558 --> 00:23:39.059 of ongoing work in the lab.

NOTE Confidence: 0.844605326

00:23:39.060 --> 00:23:40.660 We're really interested in understanding

NOTE Confidence: 0.844605326

00:23:40.660 --> 00:23:42.260 the specificity of this process.

NOTE Confidence: 0.844605326

00:23:42.260 --> 00:23:44.168 So I remember giving this talk

NOTE Confidence: 0.844605326

00:23:44.168 --> 00:23:46.364 early on compliment work both to

NOTE Confidence: 0.844605326

00:23:46.364 --> 00:23:48.096 neuroscientists and to immunologists.

NOTE Confidence: 0.844605326

00:23:48.100 --> 00:23:49.374 And the question I always got was,

NOTE Confidence: 0.844605326

00:23:49.380 --> 00:23:50.572 well, these are secreted.

NOTE Confidence: 0.844605326

00:23:50.572 --> 00:23:52.360 How do you get any specificity

NOTE Confidence: 0.844605326

00:23:52.415 --> 00:23:54.312 in this process if they just are

NOTE Confidence: 0.844605326

00:23:54.312 --> 00:23:55.776 around and binding things in

NOTE Confidence: 0.844605326

00:23:55.776 --> 00:23:57.256 this sort of nonspecific way?

NOTE Confidence: 0.844605326

00:23:57.260 --> 00:23:58.049 I said, well,

NOTE Confidence: 0.844605326

00:23:58.049 --> 00:23:59.101 I think they're probably

NOTE Confidence: 0.844605326

00:23:59.101 --> 00:24:00.219 not binding things in it.

NOTE Confidence: 0.844605326

00:24:00.220 --> 00:24:01.860 They can be binding in a nonspecific way,

NOTE Confidence: 0.844605326

00:24:01.860 --> 00:24:02.940 but I think there could

NOTE Confidence: 0.844605326

00:24:02.940 --> 00:24:04.020 be a specificity in this,

NOTE Confidence: 0.844605326

00:24:04.020 --> 00:24:06.140 in this process and indeed.

NOTE Confidence: 0.844605326

00:24:06.140 --> 00:24:07.896 The working mechanistic model,

NOTE Confidence: 0.844605326

00:24:07.896 --> 00:24:09.652 especially bringing an activity

NOTE Confidence: 0.844605326

00:24:09.652 --> 00:24:12.004 is perhaps it's it's the case

NOTE Confidence: 0.844605326

00:24:12.004 --> 00:24:13.416 where there's some receptor,

NOTE Confidence: 0.844605326

00:24:13.420 --> 00:24:16.542 some molecular difference and

NOTE Confidence: 0.844605326

00:24:16.542 --> 00:24:18.147 the surface of synapses that's

NOTE Confidence: 0.844605326

00:24:18.147 --> 00:24:19.879 recruiting or or enabling complement

NOTE Confidence: 0.844605326

00:24:19.879 --> 00:24:21.654 to bind to certain synapses,

NOTE Confidence: 0.844605326

00:24:21.660 --> 00:24:24.340 let's say the blue ones but not the red ones.

NOTE Confidence: 0.844605326

00:24:24.340 --> 00:24:26.868 And there may also be molecules that are

NOTE Confidence: 0.844605326

00:24:26.868 --> 00:24:29.058 protecting the synapses you want to keep.

NOTE Confidence: 0.844605326

00:24:29.060 --> 00:24:31.175 Now this was a hypothesis that came out of,

NOTE Confidence: 0.844605326

00:24:31.180 --> 00:24:31.714 you know,

NOTE Confidence: 0.844605326

00:24:31.714 --> 00:24:32.782 actually I remember giving

NOTE Confidence: 0.844605326

00:24:32.782 --> 00:24:33.850 this talk to immunologists

NOTE Confidence: 0.900374925

00:24:33.894 --> 00:24:34.960 at Harvard. Early, early on,

NOTE Confidence: 0.900374925

00:24:34.960 --> 00:24:36.340 where they said, well, could there be

NOTE Confidence: 0.900374925

00:24:36.340 --> 00:24:37.800 don't eat me signals in the brain.

NOTE Confidence: 0.900374925

00:24:37.800 --> 00:24:39.319 And I didn't even know what those

NOTE Confidence: 0.900374925

00:24:39.319 --> 00:24:40.860 were because I was, you know,

NOTE Confidence: 0.900374925

00:24:40.860 --> 00:24:42.840 neuroscientist trying to be an immunologist.

NOTE Confidence: 0.900374925

00:24:42.840 --> 00:24:44.640 But it turned out I had a fantastic

NOTE Confidence: 0.900374925

00:24:44.640 --> 00:24:46.060 graduate student who wanted to learn

NOTE Confidence: 0.900374925

00:24:46.060 --> 00:24:47.440 about these don't eat me signals.

NOTE Confidence: 0.900374925

00:24:47.440 --> 00:24:49.416 And it turns out there's a whole bunch

NOTE Confidence: 0.900374925

00:24:49.416 --> 00:24:51.076 of inhibitors and don't eat me signals

NOTE Confidence: 0.900374925

00:24:51.076 --> 00:24:52.720 that when we looked in the brain,

NOTE Confidence: 0.900374925

00:24:52.720 --> 00:24:53.908 immunologists didn't pay attention

NOTE Confidence: 0.900374925

00:24:53.908 --> 00:24:54.799 to the brain.

NOTE Confidence: 0.900374925

00:24:54.800 --> 00:24:56.528 But we had antibodies and we

NOTE Confidence: 0.900374925

00:24:56.528 --> 00:24:57.680 looked by expression profiling.

NOTE Confidence: 0.900374925

00:24:57.680 --> 00:24:59.111 Well, there's a whole slew of them on the

NOTE Confidence: 0.900374925

00:24:59.111 --> 00:25:00.358 brain and we better have those there.

NOTE Confidence: 0.900374925

00:25:00.360 --> 00:25:02.656 Otherwise the compliment system is going to.

NOTE Confidence: 0.900374925

00:25:02.660 --> 00:25:04.276 Kind of will be on OverDrive and they

NOTE Confidence: 0.900374925

00:25:04.276 --> 00:25:06.178 needs to be this tightly regulated system.

NOTE Confidence: 0.900374925

00:25:06.180 --> 00:25:07.755 So just as important as

NOTE Confidence: 0.900374925

00:25:07.755 --> 00:25:08.700 having compliment there,

NOTE Confidence: 0.900374925

00:25:08.700 --> 00:25:10.098 there needs to be the regulators,

NOTE Confidence: 0.900374925

00:25:10.100 --> 00:25:12.536 the brakes that keep it from activating.

NOTE Confidence: 0.900374925

00:25:12.540 --> 00:25:13.988 And so we started looking and I'm not

NOTE Confidence: 0.900374925

00:25:13.988 --> 00:25:15.499 going to tell you about all of these,

NOTE Confidence: 0.900374925

00:25:15.500 --> 00:25:18.068 but intriguingly in addition to a bunch of

NOTE Confidence: 0.900374925

00:25:18.068 --> 00:25:20.819 don't eat me signals that we've identified,

NOTE Confidence: 0.900374925

00:25:20.820 --> 00:25:23.165 I want to show you the working

NOTE Confidence: 0.900374925

00:25:23.165 --> 00:25:25.050 model we identified for example.

NOTE Confidence: 0.900374925

00:25:25.050 --> 00:25:27.115 CD47 which is also there's been some

NOTE Confidence: 0.900374925

00:25:27.115 --> 00:25:29.230 genetics that are not as powerful but

NOTE Confidence: 0.900374925

00:25:29.230 --> 00:25:31.224 there's some some hints that CD47 serve.

NOTE Confidence: 0.900374925

00:25:31.224 --> 00:25:33.093 Alpha could be playing a role in

NOTE Confidence: 0.900374925

00:25:33.093 --> 00:25:35.074 some of these in some of these

NOTE Confidence: 0.900374925

00:25:35.074 --> 00:25:36.604 GY studies still early days.

NOTE Confidence: 0.900374925

00:25:36.610 --> 00:25:39.578 But regardless of that we showed in

NOTE Confidence: 0.900374925

00:25:39.578 --> 00:25:42.095 the brain that CD47 is a classic don't

NOTE Confidence: 0.900374925

00:25:42.095 --> 00:25:44.471 eat me signal in the immune system and

NOTE Confidence: 0.900374925

00:25:44.471 --> 00:25:46.613 it actually prevents a macrophage from

NOTE Confidence: 0.900374925

00:25:46.613 --> 00:25:48.583 eating a self cell or healthy cell.

NOTE Confidence: 0.900374925

00:25:48.583 --> 00:25:50.449 In fact healthy cells and self

NOTE Confidence: 0.900374925

00:25:50.449 --> 00:25:52.505 cells have a whole shield of don't

NOTE Confidence: 0.900374925

00:25:52.505 --> 00:25:53.930 eat me signals that say.

NOTE Confidence: 0.900374925

00:25:53.930 --> 00:25:55.694 You know what do not even come

NOTE Confidence: 0.900374925

00:25:55.694 --> 00:25:57.327 near me because I need to stay.

NOTE Confidence: 0.900374925

00:25:57.330 --> 00:25:59.143 And the idea is when they're there

NOTE Confidence: 0.900374925

00:25:59.143 --> 00:26:00.429 there's apartosis or when it's

NOTE Confidence: 0.900374925

00:26:00.429 --> 00:26:01.803 some kind of a damage signal,

NOTE Confidence: 0.900374925

00:26:01.810 --> 00:26:03.886 those get down regulated and relocalized,

NOTE Confidence: 0.900374925

00:26:03.890 --> 00:26:05.594 and it exposes parts of cells that can

NOTE Confidence: 0.900374925

00:26:05.594 --> 00:26:07.450 then lead to the removal by a macrophage.

NOTE Confidence: 0.900374925

00:26:07.450 --> 00:26:09.154 And what my graduate student went

NOTE Confidence: 0.900374925

00:26:09.154 --> 00:26:11.730 on to show is CD47 is one of those

NOTE Confidence: 0.900374925

00:26:11.730 --> 00:26:13.170 signals highly expressed in neurons.

NOTE Confidence: 0.900374925

00:26:13.170 --> 00:26:14.454 Microglia have SERP Alpha,

NOTE Confidence: 0.900374925

00:26:14.454 --> 00:26:16.714 which is the receptor that recognizes that

NOTE Confidence: 0.900374925

00:26:16.714 --> 00:26:18.646 and essentially that says don't eat me.

NOTE Confidence: 0.900374925

00:26:18.650 --> 00:26:20.470 And one model is that.

NOTE Confidence: 0.900374925

00:26:20.470 --> 00:26:22.843 The stronger synapses have a lot of

NOTE Confidence: 0.900374925

00:26:22.843 --> 00:26:24.848 those protective molecules so that even

NOTE Confidence: 0.900374925

00:26:24.848 --> 00:26:26.708 if microglia are tagged by complement,

NOTE Confidence: 0.900374925

00:26:26.710 --> 00:26:28.510 synapses have complement on them.

NOTE Confidence: 0.900374925

00:26:28.510 --> 00:26:29.550 They won't get removed.

NOTE Confidence: 0.900374925

00:26:29.550 --> 00:26:31.110 And that's again a working model.

NOTE Confidence: 0.900374925

00:26:31.110 --> 00:26:32.629 But we do have data to support

NOTE Confidence: 0.900374925

00:26:32.629 --> 00:26:33.974 that idea because when we knock

NOTE Confidence: 0.900374925

00:26:33.974 --> 00:26:35.270 out the don't eat me signals,

NOTE Confidence: 0.900374925

00:26:35.270 --> 00:26:37.734 there's not only do we lose that

NOTE Confidence: 0.900374925

00:26:37.734 --> 00:26:38.790 activity dependent specificity,

NOTE Confidence: 0.900374925

00:26:38.790 --> 00:26:41.110 but you get an over pruning as well.

NOTE Confidence: 0.900374925

00:26:41.110 --> 00:26:41.954 So that's one example.

NOTE Confidence: 0.900374925

00:26:41.954 --> 00:26:43.478 We have others that I'm not going

NOTE Confidence: 0.900374925

00:26:43.478 --> 00:26:44.768 to tell you about today because

NOTE Confidence: 0.900374925

00:26:44.768 --> 00:26:46.428 that's what I talked about yesterday.

NOTE Confidence: 0.900374925

00:26:46.430 --> 00:26:47.907 But I want to tell you about

NOTE Confidence: 0.900374925

00:26:47.907 --> 00:26:48.830 another one and some,

NOTE Confidence: 0.900374925

00:26:48.830 --> 00:26:50.050 if you guys are paying

NOTE Confidence: 0.900374925

00:26:50.050 --> 00:26:51.270 attention to my second slide,

NOTE Confidence: 0.9603804

00:26:51.270 --> 00:26:52.618 you might have remembered

NOTE Confidence: 0.9603804

00:26:52.618 --> 00:26:54.222 another molecule called CSM D1,

NOTE Confidence: 0.9603804

00:26:54.222 --> 00:26:56.865 which is a gene that came up really

NOTE Confidence: 0.9603804

00:26:56.865 --> 00:26:58.269 early in GWAS schizophrenia.

NOTE Confidence: 0.9603804

00:26:58.270 --> 00:27:00.002 That's been largely nothing

NOTE Confidence: 0.9603804

00:27:00.002 --> 00:27:02.360 known about CSM D1 in the brain.

NOTE Confidence: 0.9603804

00:27:02.360 --> 00:27:04.340 And so there was a I went to a meeting

NOTE Confidence: 0.9603804

00:27:04.392 --> 00:27:06.309 in this is like a small world that I

NOTE Confidence: 0.9603804

00:27:06.309 --> 00:27:08.080 went to a compliment meeting in in

NOTE Confidence: 0.9603804

00:27:08.080 --> 00:27:10.280 Greece would not a bad place for a meeting.

NOTE Confidence: 0.9603804

00:27:10.280 --> 00:27:11.904 And I met this woman who scientists

NOTE Confidence: 0.9603804

00:27:11.904 --> 00:27:14.046 who came up to me and said I've been

NOTE Confidence: 0.9603804

00:27:14.046 --> 00:27:15.605 really wanting to meet you because

NOTE Confidence: 0.9603804

00:27:15.605 --> 00:27:17.945 we've been studying the CSM D1 and

NOTE Confidence: 0.9603804

00:27:17.945 --> 00:27:20.482 we have evidence that inhibits C4 in

NOTE Confidence: 0.9603804

00:27:20.482 --> 00:27:22.215 not in the brain but in a in a test

NOTE Confidence: 0.9603804

00:27:22.215 --> 00:27:23.983 tube in the in the in the laboratory

NOTE Confidence: 0.9603804

00:27:23.983 --> 00:27:25.793 and and it's a putative compliment

NOTE Confidence: 0.9603804

00:27:25.793 --> 00:27:26.714 inhibitor I'm like.

NOTE Confidence: 0.9603804

00:27:26.720 --> 00:27:27.884 Well, this is amazing.

NOTE Confidence: 0.9603804

00:27:27.884 --> 00:27:29.339 So we started talking more

NOTE Confidence: 0.9603804

00:27:29.339 --> 00:27:30.838 and and for many reasons,

NOTE Confidence: 0.9603804

00:27:30.840 --> 00:27:32.160 we started thinking that this

NOTE Confidence: 0.9603804

00:27:32.160 --> 00:27:33.480 would be an interesting molecule,

NOTE Confidence: 0.9603804

00:27:33.480 --> 00:27:34.518 not just because of the genetics,

NOTE Confidence: 0.9603804

00:27:34.520 --> 00:27:36.256 but if it is involved in the

NOTE Confidence: 0.9603804

00:27:36.256 --> 00:27:37.000 classical complement cascade,

NOTE Confidence: 0.9603804

00:27:37.000 --> 00:27:38.078 we want to know more about what

NOTE Confidence: 0.9603804

00:27:38.078 --> 00:27:38.800 it might be doing.

NOTE Confidence: 0.9603804

00:27:38.800 --> 00:27:39.840 And this is ongoing work.

NOTE Confidence: 0.9603804

00:27:39.840 --> 00:27:40.920 The paper's on bio archive,

NOTE Confidence: 0.9603804

00:27:40.920 --> 00:27:42.156 but we're just revising it now.

NOTE Confidence: 0.9603804

00:27:42.160 --> 00:27:42.960 So there's more to come,

NOTE Confidence: 0.9603804

00:27:42.960 --> 00:27:44.380 but just want to highlight

NOTE Confidence: 0.9603804

00:27:44.380 --> 00:27:46.156 this work and again how, how?

NOTE Confidence: 0.9603804

00:27:46.156 --> 00:27:46.512 Again,

NOTE Confidence: 0.9603804

00:27:46.512 --> 00:27:48.292 two now common variants are

NOTE Confidence: 0.9603804

00:27:48.292 --> 00:27:50.171 coming together that suggests some

NOTE Confidence: 0.9603804

00:27:50.171 --> 00:27:52.036 role in the complement system.

NOTE Confidence: 0.9603804

00:27:52.040 --> 00:27:53.734 So CSM D1 is a well localized

NOTE Confidence: 0.9603804

00:27:53.734 --> 00:27:55.645 US signal as I mentioned with

NOTE Confidence: 0.9603804

00:27:55.645 --> 00:27:57.520 schizophrenia risk on chromosome 8.

NOTE Confidence: 0.9603804

00:27:57.520 --> 00:27:59.277 And although it's enriched in the brain,

NOTE Confidence: 0.9603804

00:27:59.280 --> 00:28:01.122 in fact if you look expression

NOTE Confidence: 0.9603804

00:28:01.122 --> 00:28:03.159 by protein and gene and and RNA,

NOTE Confidence: 0.9603804

00:28:03.160 --> 00:28:03.985 there's unlike C4,

NOTE Confidence: 0.9603804

00:28:03.985 --> 00:28:05.910 it is in nowhere else except the

NOTE Confidence: 0.9603804

00:28:05.971 --> 00:28:08.075 testes like it is blazing in the brain.

NOTE Confidence: 0.9603804

00:28:08.080 --> 00:28:08.887 So therefore, wow,

NOTE Confidence: 0.9603804

00:28:08.887 --> 00:28:11.080 how can't we know what this thing does?

NOTE Confidence: 0.9603804

00:28:11.080 --> 00:28:11.490 Okay.

NOTE Confidence: 0.9603804

00:28:11.490 --> 00:28:14.360 And so we don't know about lost,

NOTE Confidence: 0.9603804

00:28:14.360 --> 00:28:16.238 we don't know directionality or anything.

NOTE Confidence: 0.9603804

00:28:16.240 --> 00:28:17.422 There's a lot more genetics to

NOTE Confidence: 0.9603804

00:28:17.422 --> 00:28:18.878 be done in terms of the mapping,

NOTE Confidence: 0.9603804

00:28:18.880 --> 00:28:21.064 but we wanted to look more closely

NOTE Confidence: 0.9603804

00:28:21.064 --> 00:28:22.280 at this and so.

NOTE Confidence: 0.9603804

00:28:22.280 --> 00:28:23.220 A postdoc, Matt Johnson,

NOTE Confidence: 0.9603804

00:28:23.220 --> 00:28:24.932 now a group leader at the Stanley

NOTE Confidence: 0.9603804

00:28:24.932 --> 00:28:26.426 Center who's been Co leading this

NOTE Confidence: 0.9603804

00:28:26.426 --> 00:28:28.203 with me and collaboration with Steve

NOTE Confidence: 0.9603804

00:28:28.203 --> 00:28:29.828 Mccarroll and our graduate student

NOTE Confidence: 0.9603804

00:28:29.828 --> 00:28:32.556 Matt Baum is an MDPHD student who finished,

NOTE Confidence: 0.9603804

00:28:32.560 --> 00:28:33.970 I'll tell you about what he

NOTE Confidence: 0.9603804

00:28:33.970 --> 00:28:34.675 what he uncovered.

NOTE Confidence: 0.9603804

00:28:34.680 --> 00:28:35.880 So it turns out,

NOTE Confidence: 0.9603804

00:28:35.880 --> 00:28:37.080 see as I mentioned,

NOTE Confidence: 0.9603804

00:28:37.080 --> 00:28:39.138 it's very highly expressed both at the

NOTE Confidence: 0.9603804

00:28:39.138 --> 00:28:41.119 RNA and protein level in the brain.

NOTE Confidence: 0.9603804

00:28:41.120 --> 00:28:42.280 So that was, you know,

NOTE Confidence: 0.9603804

00:28:42.280 --> 00:28:44.380 obviously something worth looking at no

NOTE Confidence: 0.9603804

00:28:44.380 --> 00:28:47.080 matter what but when we started looking.

NOTE Confidence: 0.9603804

00:28:47.080 --> 00:28:48.880 Thanks to an amazing antibody

NOTE Confidence: 0.9603804

00:28:48.880 --> 00:28:50.680 that we had access to,

NOTE Confidence: 0.9603804

00:28:50.680 --> 00:28:53.040 we started staining and obtained

NOTE Confidence: 0.9603804

00:28:53.040 --> 00:28:53.964 ACSM D1 knockout mouse.

NOTE Confidence: 0.9603804

00:28:53.964 --> 00:28:56.358 Just to ask just like we did with complement,

NOTE Confidence: 0.9603804

00:28:56.360 --> 00:28:57.221 you know what,

NOTE Confidence: 0.9603804

00:28:57.221 --> 00:28:58.656 what's the phenotypes and where

NOTE Confidence: 0.9603804

00:28:58.656 --> 00:28:59.720 is the protein.

NOTE Confidence: 0.9603804

00:28:59.720 --> 00:29:01.211 So that was also a great tool

NOTE Confidence: 0.9603804

00:29:01.211 --> 00:29:02.521 for our antibody because the

NOTE Confidence: 0.9603804

00:29:02.521 --> 00:29:03.757 antibody is really specific,

NOTE Confidence: 0.9603804

00:29:03.760 --> 00:29:05.279 not only does it light up the

NOTE Confidence: 0.9603804

00:29:05.279 --> 00:29:06.508 brain in interesting regions of

NOTE Confidence: 0.9603804

00:29:06.508 --> 00:29:07.833 the brain especially you could

NOTE Confidence: 0.9603804

00:29:07.833 --> 00:29:09.120 see hippocampus and certain areas

NOTE Confidence: 0.9603804

00:29:09.120 --> 00:29:10.235 of the brain at lomag.

NOTE Confidence: 0.912455328571429

00:29:10.240 --> 00:29:12.404 But if you really is a man, I hard to see.

NOTE Confidence: 0.912455328571429

00:29:12.404 --> 00:29:14.336 We saw a lot of punctate staining

NOTE Confidence: 0.912455328571429

00:29:14.336 --> 00:29:16.446 and it colocalizes with subsets.

NOTE Confidence: 0.912455328571429

00:29:16.450 --> 00:29:18.890 Of inhibitory and excitatory synopses.

NOTE Confidence: 0.912455328571429

00:29:18.890 --> 00:29:21.090 So it's at synopsis not only at synapses,

NOTE Confidence: 0.912455328571429

00:29:21.090 --> 00:29:22.637 but we have some data that's enriched

NOTE Confidence: 0.912455328571429

00:29:22.637 --> 00:29:23.804 in synopsis because we've done

NOTE Confidence: 0.912455328571429

00:29:23.804 --> 00:29:24.964 some synapticome preps as well,

NOTE Confidence: 0.912455328571429

00:29:24.970 --> 00:29:25.930 which I'm not going to tell you about,

NOTE Confidence: 0.912455328571429

00:29:25.930 --> 00:29:27.906 but it's in the paper actually.

NOTE Confidence: 0.912455328571429

00:29:27.906 --> 00:29:28.610 This might be it.

NOTE Confidence: 0.912455328571429

00:29:28.610 --> 00:29:29.198 Yes, it is. OK.

NOTE Confidence: 0.912455328571429

00:29:29.198 --> 00:29:30.443 So there is a little bit of data

NOTE Confidence: 0.912455328571429

00:29:30.443 --> 00:29:31.409 there to show that it's an,

NOTE Confidence: 0.912455328571429

00:29:31.410 --> 00:29:33.210 it's an enriched in the synapticomes.

NOTE Confidence: 0.912455328571429

00:29:33.210 --> 00:29:34.350 So again at the right

NOTE Confidence: 0.912455328571429

00:29:34.350 --> 00:29:35.490 time and the right place,

NOTE Confidence: 0.912455328571429

00:29:35.490 --> 00:29:37.050 nothing known really about its biology,

NOTE Confidence: 0.912455328571429

00:29:37.050 --> 00:29:39.185 but that one interaction at the compliment

NOTE Confidence: 0.912455328571429

00:29:39.185 --> 00:29:41.303 meeting in Greece made me start to think

NOTE Confidence: 0.912455328571429

00:29:41.303 --> 00:29:43.517 about could the two be related in some way.

NOTE Confidence: 0.912455328571429

00:29:43.520 --> 00:29:45.320 And so the idea would be, okay,

NOTE Confidence: 0.912455328571429

00:29:45.320 --> 00:29:48.200 we already know that C4 is high and that

NOTE Confidence: 0.912455328571429

00:29:48.274 --> 00:29:51.200 leads to activation of the cobman cascade.

NOTE Confidence: 0.912455328571429

00:29:51.200 --> 00:29:53.657 At least in animal models that could

NOTE Confidence: 0.912455328571429

00:29:53.657 --> 00:29:56.008 lead to over pruning could C4C,

NOTE Confidence: 0.912455328571429

00:29:56.008 --> 00:29:56.584 SM D1.

NOTE Confidence: 0.912455328571429

00:29:56.584 --> 00:29:58.312 Which the other reason why this

NOTE Confidence: 0.912455328571429

00:29:58.312 --> 00:30:00.517 is really exciting is it is

NOTE Confidence: 0.912455328571429

00:30:00.517 --> 00:30:01.993 a huge extracellular domain,

NOTE Confidence: 0.912455328571429

00:30:02.000 --> 00:30:05.138 it's giant and it has a the reason

NOTE Confidence: 0.912455328571429

00:30:05.138 --> 00:30:07.604 why it's called CSM D1 is it's

NOTE Confidence: 0.912455328571429

00:30:07.604 --> 00:30:10.010 it's got cub and sushi domains.

NOTE Confidence: 0.912455328571429

00:30:10.010 --> 00:30:11.170 And these are the domains

NOTE Confidence: 0.912455328571429

00:30:11.170 --> 00:30:12.330 that are expressed in many,

NOTE Confidence: 0.912455328571429

00:30:12.330 --> 00:30:13.116 many complement inhibitors

NOTE Confidence: 0.912455328571429

00:30:13.116 --> 00:30:14.164 in the immune system.

NOTE Confidence: 0.912455328571429

00:30:14.170 --> 00:30:16.498 And that's why my my colleague

NOTE Confidence: 0.912455328571429

00:30:16.498 --> 00:30:17.838 was interested in it.

NOTE Confidence: 0.912455328571429

00:30:17.838 --> 00:30:20.050 And so that led us to wonder,

NOTE Confidence: 0.912455328571429

00:30:20.050 --> 00:30:22.906 could could it be that what csmd one

NOTE Confidence: 0.912455328571429

00:30:22.906 --> 00:30:25.128 is normally doing is putting the

NOTE Confidence: 0.912455328571429

00:30:25.128 --> 00:30:28.020 brakes on C4 and keeping it in check?

NOTE Confidence: 0.912455328571429

00:30:28.020 --> 00:30:28.526 Therefore,

NOTE Confidence: 0.912455328571429

00:30:28.526 --> 00:30:32.146 if there was a genetic mutation or loss

NOTE Confidence: 0.912455328571429

00:30:32.146 --> 00:30:35.100 of function or an ability to disrupt csmd,

NOTE Confidence: 0.912455328571429

00:30:35.100 --> 00:30:36.640 one's function could then that

NOTE Confidence: 0.912455328571429

00:30:36.640 --> 00:30:38.180 therefore that would lead to

NOTE Confidence: 0.912455328571429

00:30:38.238 --> 00:30:39.858 again an over activation of C4.

NOTE Confidence: 0.912455328571429

00:30:39.860 --> 00:30:40.113 Again,

NOTE Confidence: 0.912455328571429

00:30:40.113 --> 00:30:41.884 this is all hypothesis and I'll just

NOTE Confidence: 0.912455328571429

00:30:41.884 --> 00:30:43.713 tell you the way we've been testing

NOTE Confidence: 0.912455328571429

00:30:43.713 --> 00:30:45.280 it and it's still ongoing work.

NOTE Confidence: 0.912455328571429

00:30:45.280 --> 00:30:46.760 One way we can also look at this

NOTE Confidence: 0.912455328571429

00:30:46.760 --> 00:30:48.402 to see whether there'd be more

NOTE Confidence: 0.912455328571429

00:30:48.402 --> 00:30:49.922 complement activation or more tagging

NOTE Confidence: 0.912455328571429

00:30:49.922 --> 00:30:51.759 of complement was this experiment.

NOTE Confidence: 0.912455328571429

00:30:51.760 --> 00:30:54.037 We not only do we have the knockout mice,

NOTE Confidence: 0.912455328571429

00:30:54.040 --> 00:30:55.881 so we can look at whether there's

NOTE Confidence: 0.912455328571429

00:30:55.881 --> 00:30:57.045 too much complement tagging

NOTE Confidence: 0.912455328571429

00:30:57.045 --> 00:30:58.317 and removal of synapses.

NOTE Confidence: 0.912455328571429

00:30:58.320 --> 00:31:00.258 We also took advantage of IPS

NOTE Confidence: 0.912455328571429

00:31:00.258 --> 00:31:02.242 stem cell models where we could

NOTE Confidence: 0.912455328571429

00:31:02.242 --> 00:31:04.360 use isogenic controls in a CSMD,

NOTE Confidence: 0.912455328571429

00:31:04.360 --> 00:31:06.040 knockout neuronal differentiation

NOTE Confidence: 0.912455328571429

00:31:06.040 --> 00:31:08.840 these N G2 neuron protocols.

NOTE Confidence: 0.912455328571429

00:31:08.840 --> 00:31:10.820 And basically did a very classic

NOTE Confidence: 0.912455328571429

00:31:10.820 --> 00:31:12.526 immunology experiment where we could

NOTE Confidence: 0.912455328571429

00:31:12.526 --> 00:31:14.476 sensitize with an anti surface antibody

NOTE Confidence: 0.912455328571429

00:31:14.476 --> 00:31:16.558 which would then bind to the surface.

NOTE Confidence: 0.912455328571429

00:31:16.560 --> 00:31:18.468 And then we wanted to know

NOTE Confidence: 0.912455328571429

00:31:18.468 --> 00:31:20.359 if we then add tag C3,

NOTE Confidence: 0.912455328571429

00:31:20.360 --> 00:31:22.803 do we get more tagging or the

NOTE Confidence: 0.912455328571429

00:31:22.803 --> 00:31:24.488 localization of synopses with C3

NOTE Confidence: 0.912455328571429

00:31:24.488 --> 00:31:26.304 in mice that don't have CSM D1,

NOTE Confidence: 0.912455328571429

00:31:26.304 --> 00:31:26.880 not sorry mice,

NOTE Confidence: 0.912455328571429

00:31:26.880 --> 00:31:28.680 but yes mice but in this case cells.

NOTE Confidence: 0.912455328571429

00:31:28.680 --> 00:31:28.972 OK.

NOTE Confidence: 0.912455328571429

00:31:28.972 --> 00:31:31.016 So this is just an example of

NOTE Confidence: 0.912455328571429

00:31:31.016 --> 00:31:33.068 the type of assay and indeed.

NOTE Confidence: 0.912455328571429

00:31:33.070 --> 00:31:34.510 Much more data on this than I'm showing you,

NOTE Confidence: 0.912455328571429

00:31:34.510 --> 00:31:36.406 but just to illustrate what what

NOTE Confidence: 0.912455328571429

00:31:36.406 --> 00:31:38.569 Matt and others found was there was

NOTE Confidence: 0.912455328571429

00:31:38.569 --> 00:31:40.529 a sort of a selective and enhanced

NOTE Confidence: 0.928229943333333

00:31:40.596 --> 00:31:42.963 tagging of C3 in the neurites even in a

NOTE Confidence: 0.928229943333333

00:31:42.963 --> 00:31:46.266 mixed culture that didn't have CSCSM D1.

NOTE Confidence: 0.928229943333333

00:31:46.270 --> 00:31:47.788 So that was proof, not proof,

NOTE Confidence: 0.928229943333333

00:31:47.790 --> 00:31:49.795 but certainly evidence that suggests

NOTE Confidence: 0.928229943333333

00:31:49.795 --> 00:31:51.800 that it's somehow regulating complement

NOTE Confidence: 0.928229943333333

00:31:51.856 --> 00:31:54.040 deposition and we think activation to

NOTE Confidence: 0.928229943333333

00:31:54.040 --> 00:31:55.710 other experiments we're working on.

NOTE Confidence: 0.928229943333333

00:31:55.710 --> 00:31:58.190 And then in the in the mouse model,

NOTE Confidence: 0.928229943333333

00:31:58.190 --> 00:31:59.718 we I'm not going to show all the

NOTE Confidence: 0.928229943333333

00:31:59.718 --> 00:32:01.147 data in the interest of time.

NOTE Confidence: 0.928229943333333

00:32:01.150 --> 00:32:02.974 But we went on and did the same

NOTE Confidence: 0.928229943333333

00:32:02.974 --> 00:32:05.050 kind of experiments by looking at

NOTE Confidence: 0.928229943333333

00:32:05.050 --> 00:32:06.733 complement and localization at synapses.

NOTE Confidence: 0.928229943333333

00:32:06.733 --> 00:32:09.199 And we wanted to know do we see

NOTE Confidence: 0.928229943333333

00:32:09.199 --> 00:32:10.704 more complement tagging of synapses

NOTE Confidence: 0.928229943333333

00:32:10.704 --> 00:32:12.990 in the in the CSM D1 knockout mice

NOTE Confidence: 0.928229943333333

00:32:12.990 --> 00:32:15.111 and in the visual system at least

NOTE Confidence: 0.928229943333333

00:32:15.111 --> 00:32:16.867 has increased complement tagging.

NOTE Confidence: 0.928229943333333

00:32:16.870 --> 00:32:18.870 We see an enhanced refinement by a retina,

NOTE Confidence: 0.928229943333333

00:32:18.870 --> 00:32:19.802 geniculate experiments,

NOTE Confidence: 0.928229943333333

00:32:19.802 --> 00:32:22.132 decrease in synapses and some

NOTE Confidence: 0.928229943333333

00:32:22.132 --> 00:32:24.269 electrophysiology work that's in progress.

NOTE Confidence: 0.928229943333333

00:32:24.270 --> 00:32:26.170 So together suggesting that some

NOTE Confidence: 0.928229943333333

00:32:26.170 --> 00:32:28.844 interesting phenotypes and that may be 1

NOTE Confidence: 0.928229943333333

00:32:28.844 --> 00:32:30.639 mechanisms to the complement inhibition.

NOTE Confidence: 0.928229943333333

00:32:30.640 --> 00:32:32.989 And so that and we also have some in

NOTE Confidence: 0.928229943333333

00:32:32.989 --> 00:32:35.668 vitro and in vivo work ongoing that also

NOTE Confidence: 0.928229943333333

00:32:35.668 --> 00:32:37.722 show that microglia can overprune or

NOTE Confidence: 0.928229943333333

00:32:37.722 --> 00:32:40.256 engulf much like the C4A mice we're doing.

NOTE Confidence: 0.928229943333333

00:32:40.256 --> 00:32:42.705 So that's sort of the working model and

NOTE Confidence: 0.928229943333333

00:32:42.705 --> 00:32:44.945 in no way does this explain that this

NOTE Confidence: 0.928229943333333

00:32:45.011 --> 00:32:47.398 is the mechanism that that the genetics,

NOTE Confidence: 0.928229943333333

00:32:47.400 --> 00:32:49.353 this is the only way this might be working.

NOTE Confidence: 0.928229943333333

00:32:49.360 --> 00:32:52.376 But I think it is together suggest a

NOTE Confidence: 0.928229943333333

00:32:52.376 --> 00:32:54.640 mechanistic model that we're going to

NOTE Confidence: 0.928229943333333

00:32:54.640 --> 00:32:56.736 continue to test in in various ways.

NOTE Confidence: 0.928229943333333

00:32:56.736 --> 00:32:58.989 So this is a lot of the basic

NOTE Confidence: 0.928229943333333

00:32:58.989 --> 00:33:01.313 science that I wanted to start with,

NOTE Confidence: 0.928229943333333

00:33:01.320 --> 00:33:02.625 but now I want to zoom out and I

NOTE Confidence: 0.928229943333333

00:33:02.625 --> 00:33:04.065 want to talk more about the timing

NOTE Confidence: 0.928229943333333

00:33:04.065 --> 00:33:05.483 part because that's the part that

NOTE Confidence: 0.928229943333333

00:33:05.483 --> 00:33:06.559 I'm particularly interested in,

NOTE Confidence: 0.928229943333333

00:33:06.560 --> 00:33:09.176 is understanding why,

NOTE Confidence: 0.928229943333333

00:33:09.176 --> 00:33:10.920 for example,

NOTE Confidence: 0.928229943333333

00:33:10.920 --> 00:33:15.143 adolescence is a is a time where we know is

NOTE Confidence: 0.928229943333333

00:33:15.143 --> 00:33:18.230 an onset for a lot of these mental illnesses.

NOTE Confidence: 0.928229943333333

00:33:18.230 --> 00:33:19.376 In particular,

NOTE Confidence: 0.928229943333333

00:33:19.376 --> 00:33:19.949 schizophrenia,

NOTE Confidence: 0.928229943333333

00:33:19.949 --> 00:33:22.016 even even though potentially

NOTE Confidence: 0.928229943333333

00:33:22.016 --> 00:33:23.746 there could be issues earlier,

NOTE Confidence: 0.928229943333333

00:33:23.750 --> 00:33:25.080 but the emergence tends to

NOTE Confidence: 0.928229943333333

00:33:25.080 --> 00:33:26.144 happen in laid adolescence,

NOTE Confidence: 0.928229943333333

00:33:26.150 --> 00:33:27.255 early adulthood and this is

NOTE Confidence: 0.928229943333333

00:33:27.255 --> 00:33:28.630 true of other things as well.

NOTE Confidence: 0.928229943333333

00:33:28.630 --> 00:33:30.373 So that raised all kind of questions

NOTE Confidence: 0.928229943333333

00:33:30.373 --> 00:33:32.029 as a developmental neurobiologist was,

NOTE Confidence: 0.928229943333333

00:33:32.030 --> 00:33:33.806 could there have always been issues

NOTE Confidence: 0.928229943333333

00:33:33.806 --> 00:33:35.371 but then something kind of opens

NOTE Confidence: 0.928229943333333

00:33:35.371 --> 00:33:36.918 up and and it emerges at this

NOTE Confidence: 0.928229943333333

00:33:36.918 --> 00:33:38.982 time in adolescence or is there

NOTE Confidence: 0.928229943333333

00:33:38.982 --> 00:33:40.546 actually something happening during

NOTE Confidence: 0.928229943333333

00:33:40.546 --> 00:33:42.108 adolescence that leads to that?

NOTE Confidence: 0.928229943333333

00:33:42.110 --> 00:33:43.104 And so this is now in the

NOTE Confidence: 0.928229943333333

00:33:43.104 --> 00:33:43.870 last part of my talk,

NOTE Confidence: 0.928229943333333

00:33:43.870 --> 00:33:45.350 I want to switch down to this part,

NOTE Confidence: 0.928229943333333

00:33:45.350 --> 00:33:46.610 the harder part,

NOTE Confidence: 0.928229943333333

00:33:46.610 --> 00:33:48.710 understanding which circuits are relevant,

NOTE Confidence: 0.928229943333333

00:33:48.710 --> 00:33:51.350 which brain regions and the timing.

NOTE Confidence: 0.928229943333333

00:33:51.350 --> 00:33:53.177 And this is really trying to get

NOTE Confidence: 0.928229943333333

00:33:53.177 --> 00:33:55.416 us to now get into the identifying

NOTE Confidence: 0.928229943333333

00:33:55.416 --> 00:33:57.146 the circus in the timing.

NOTE Confidence: 0.928229943333333

00:33:57.150 --> 00:33:58.886 So then we can start doing our

NOTE Confidence: 0.928229943333333

00:33:58.886 --> 00:34:00.210 perturbations of our mechanisms and

NOTE Confidence: 0.928229943333333

00:34:00.210 --> 00:34:02.314 then start to know what see what things

NOTE Confidence: 0.928229943333333

00:34:02.364 --> 00:34:04.065 to read out in terms of phenotypes.

NOTE Confidence: 0.928229943333333

00:34:04.070 --> 00:34:06.030 So it's around that time.

NOTE Confidence: 0.928229943333333

00:34:06.030 --> 00:34:07.386 When we realized we can't just

NOTE Confidence: 0.928229943333333

00:34:07.386 --> 00:34:08.670 study the visual system forever,

NOTE Confidence: 0.928229943333333

00:34:08.670 --> 00:34:10.270 even though I love it,

NOTE Confidence: 0.928229943333333

00:34:10.270 --> 00:34:11.926 I started collaborating with

NOTE Confidence: 0.928229943333333

00:34:11.926 --> 00:34:13.996 auto sabertini's lab and we

NOTE Confidence: 0.928229943333333

00:34:13.996 --> 00:34:15.463 recruited a terrific pH,

NOTE Confidence: 0.928229943333333

00:34:15.463 --> 00:34:16.169 now postdoc,

NOTE Confidence: 0.928229943333333

00:34:16.169 --> 00:34:18.214 who was a postdoc called Kevin

NOTE Confidence: 0.928229943333333

00:34:18.214 --> 00:34:20.510 Mastro to join our labs to work

NOTE Confidence: 0.892000614285714

00:34:20.580 --> 00:34:22.160 together on this project.

NOTE Confidence: 0.892000614285714

00:34:22.160 --> 00:34:24.488 And in particular we wanted to try to

NOTE Confidence: 0.892000614285714

00:34:24.488 --> 00:34:26.550 better understand and define the normal

NOTE Confidence: 0.892000614285714

00:34:26.550 --> 00:34:28.325 developmental refinement and and changes

NOTE Confidence: 0.892000614285714

00:34:28.325 --> 00:34:30.327 that are going on during adolescence

NOTE Confidence: 0.892000614285714

00:34:30.327 --> 00:34:32.345 in particular in the frontal cortex,

NOTE Confidence: 0.892000614285714

00:34:32.345 --> 00:34:34.470 the prefrontal cortex advice and

NOTE Confidence: 0.892000614285714

00:34:34.470 --> 00:34:37.214 ultimately in human and and non human

NOTE Confidence: 0.892000614285714

00:34:37.214 --> 00:34:39.960 primates which which is not an easy thing.

NOTE Confidence: 0.892000614285714

00:34:39.960 --> 00:34:41.689 And and I talked to Amy and

NOTE Confidence: 0.892000614285714

00:34:41.689 --> 00:34:42.760 many others about this,

NOTE Confidence: 0.892000614285714

00:34:42.760 --> 00:34:44.440 but I'm going to tell you about some

NOTE Confidence: 0.892000614285714

00:34:44.440 --> 00:34:46.297 of the the ways we're going about it

NOTE Confidence: 0.892000614285714

00:34:46.297 --> 00:34:48.210 today and this is all unpublished and

NOTE Confidence: 0.892000614285714

00:34:48.210 --> 00:34:50.376 ongoing work and I'm happy to to get

NOTE Confidence: 0.892000614285714

00:34:50.376 --> 00:34:52.098 feedback from this group but I think.

NOTE Confidence: 0.892000614285714

00:34:52.100 --> 00:34:53.652 You know, we've done a lot of our

NOTE Confidence: 0.892000614285714

00:34:53.652 --> 00:34:55.230 work over here in early development

NOTE Confidence: 0.892000614285714

00:34:55.230 --> 00:34:56.940 and of course that's super important.

NOTE Confidence: 0.892000614285714

00:34:56.940 --> 00:34:58.697 But we wanted to better understand sort

NOTE Confidence: 0.892000614285714

00:34:58.697 --> 00:35:00.898 of this next stage and we wanted to again,

NOTE Confidence: 0.892000614285714

00:35:00.900 --> 00:35:03.420 after the sensory systems develop and refine,

NOTE Confidence: 0.892000614285714

00:35:03.420 --> 00:35:05.220 now we want to get to the prefrontal,

NOTE Confidence: 0.892000614285714

00:35:05.220 --> 00:35:06.788 which began as the last area of the

NOTE Confidence: 0.892000614285714

00:35:06.788 --> 00:35:08.609 brain to myelinate and mature and all

NOTE Confidence: 0.892000614285714

00:35:08.609 --> 00:35:10.310 those connections are still being built.

NOTE Confidence: 0.892000614285714

00:35:10.310 --> 00:35:11.950 So we wanted to zone in on adolescence,

NOTE Confidence: 0.892000614285714

00:35:11.950 --> 00:35:13.598 but to do that we need to define

NOTE Confidence: 0.892000614285714

00:35:13.598 --> 00:35:15.324 what do we mean by adolescence and

NOTE Confidence: 0.892000614285714

00:35:15.324 --> 00:35:17.427 start to do what we've done in the

NOTE Confidence: 0.892000614285714

00:35:17.427 --> 00:35:18.999 visual system in the prefrontal and

NOTE Confidence: 0.892000614285714

00:35:18.999 --> 00:35:20.990 and so then we can start to ask, OK,

NOTE Confidence: 0.892000614285714

00:35:20.990 --> 00:35:22.270 how does environmental stressors,

NOTE Confidence: 0.892000614285714

00:35:22.270 --> 00:35:25.138 how do genetic stressors at different

NOTE Confidence: 0.892000614285714

00:35:25.138 --> 00:35:27.050 times impact circuit maturation

NOTE Confidence: 0.892000614285714

00:35:27.125 --> 00:35:28.790 and ultimately behavior.

NOTE Confidence: 0.892000614285714

00:35:28.790 --> 00:35:30.414 So this is before we could do any

NOTE Confidence: 0.892000614285714

00:35:30.414 --> 00:35:32.274 of that we needed to establish

NOTE Confidence: 0.892000614285714

00:35:32.274 --> 00:35:33.678 the neurotypical development and

NOTE Confidence: 0.892000614285714

00:35:33.678 --> 00:35:35.175 understand some of those milestones

NOTE Confidence: 0.892000614285714

00:35:35.175 --> 00:35:37.286 and we're doing it not only in mice.

NOTE Confidence: 0.892000614285714

00:35:37.286 --> 00:35:38.790 But through collaborations and

NOTE Confidence: 0.892000614285714

00:35:38.790 --> 00:35:40.670 work at the Stanley Center,

NOTE Confidence: 0.892000614285714

00:35:40.670 --> 00:35:42.122 we have a marmoset colony and

NOTE Confidence: 0.892000614285714

00:35:42.122 --> 00:35:43.390 we've been trying to have,

NOTE Confidence: 0.892000614285714

00:35:43.390 --> 00:35:45.334 we have a smaller colony devoted

NOTE Confidence: 0.892000614285714

00:35:45.334 --> 00:35:46.630 to these developmental studies.

NOTE Confidence: 0.892000614285714

00:35:46.630 --> 00:35:48.151 Go Ping Feng and many others at the road

NOTE Confidence: 0.892000614285714

00:35:48.151 --> 00:35:49.829 are leading the charge with the marmosets.

NOTE Confidence: 0.892000614285714

00:35:49.830 --> 00:35:51.237 But we've been very fortunate to be

NOTE Confidence: 0.892000614285714

00:35:51.237 --> 00:35:52.868 able to start to do some of this work.

NOTE Confidence: 0.892000614285714

00:35:52.870 --> 00:35:54.158 And this is all work led by Kevin

NOTE Confidence: 0.892000614285714

00:35:54.158 --> 00:35:55.309 Mastro that I'm telling you about.

NOTE Confidence: 0.892000614285714

00:35:55.310 --> 00:35:56.766 And there's Kevin who's amazing and he's

NOTE Confidence: 0.892000614285714

00:35:56.766 --> 00:35:58.546 on the job market and you guys should

NOTE Confidence: 0.892000614285714

00:35:58.546 --> 00:36:00.409 recruit him and Bernardo Sabatini,

NOTE Confidence: 0.892000614285714

00:36:00.409 --> 00:36:01.828 who's amazing collaborator,

NOTE Confidence: 0.892000614285714

00:36:01.830 --> 00:36:02.154 electrophysiologist.

NOTE Confidence: 0.892000614285714

00:36:02.154 --> 00:36:05.070 And So what Kevin really wanted to know is,

NOTE Confidence: 0.892000614285714

00:36:05.070 --> 00:36:07.110 you know, let's try to better

NOTE Confidence: 0.892000614285714

00:36:07.110 --> 00:36:08.470 understand again the match.

NOTE Confidence: 0.892000614285714

00:36:08.470 --> 00:36:11.190 But also we want to link this to

NOTE Confidence: 0.892000614285714

00:36:11.190 --> 00:36:13.189 behavioral readouts of decision making,

NOTE Confidence: 0.892000614285714

00:36:13.190 --> 00:36:13.860 cognitive flexibility,

NOTE Confidence: 0.892000614285714

00:36:13.860 --> 00:36:14.530 risk taking,

NOTE Confidence: 0.892000614285714

00:36:14.530 --> 00:36:16.540 things that we know are relevant

NOTE Confidence: 0.892000614285714

00:36:16.589 --> 00:36:17.869 to this adolescent window.

NOTE Confidence: 0.892000614285714

00:36:17.870 --> 00:36:19.952 And so that's going to require

NOTE Confidence: 0.892000614285714

00:36:19.952 --> 00:36:21.340 developing and identifying behavioral

NOTE Confidence: 0.892000614285714

00:36:21.394 --> 00:36:23.312 readouts that we can use in these

NOTE Confidence: 0.892000614285714

00:36:23.312 --> 00:36:25.710 different time points and and models.

NOTE Confidence: 0.892000614285714

00:36:25.710 --> 00:36:28.048 So Kevin wanted to know you know

NOTE Confidence: 0.892000614285714

00:36:28.048 --> 00:36:29.435 what circuit mechanisms support

NOTE Confidence: 0.892000614285714

00:36:29.435 --> 00:36:31.696 these changes and with a sort of

NOTE Confidence: 0.892000614285714

00:36:31.696 --> 00:36:33.028 focus on cognitive flexibility,

NOTE Confidence: 0.892000614285714

00:36:33.030 --> 00:36:36.540 readouts and decision making and so.

NOTE Confidence: 0.892000614285714

00:36:36.540 --> 00:36:38.616 The questions he's asking over what

NOTE Confidence: 0.892000614285714

00:36:38.616 --> 00:36:40.680 time skills do does behavior change

NOTE Confidence: 0.892000614285714

00:36:40.680 --> 00:36:42.380 and what circuits are changing?

NOTE Confidence: 0.892000614285714

00:36:42.380 --> 00:36:43.899 And can we link changes in circuits

NOTE Confidence: 0.892000614285714

00:36:43.899 --> 00:36:45.100 to these changes in behavior?

NOTE Confidence: 0.892000614285714

00:36:45.100 --> 00:36:45.275 Right.

NOTE Confidence: 0.892000614285714

00:36:45.275 --> 00:36:46.500 Many people are trying to do this,

NOTE Confidence: 0.942083309090909

00:36:46.500 --> 00:36:48.467 but we really want to do this

NOTE Confidence: 0.942083309090909

00:36:48.467 --> 00:36:49.740 over this developmental window.

NOTE Confidence: 0.942083309090909

00:36:49.740 --> 00:36:51.980 And then if we identify circuit changes,

NOTE Confidence: 0.942083309090909

00:36:51.980 --> 00:36:53.540 do they drive the behavioral changes?

NOTE Confidence: 0.942083309090909

00:36:53.540 --> 00:36:55.124 So then you want to go in and start

NOTE Confidence: 0.942083309090909

00:36:55.124 --> 00:36:56.926 to manipulate aspects of the circuit.

NOTE Confidence: 0.942083309090909

00:36:56.930 --> 00:36:58.463 And so we started thinking a lot

NOTE Confidence: 0.942083309090909

00:36:58.463 --> 00:36:59.783 about what time points are we

NOTE Confidence: 0.942083309090909

00:36:59.783 --> 00:37:01.218 do we talking about here and we

NOTE Confidence: 0.942083309090909

00:37:01.269 --> 00:37:02.727 of course did our due diligence,

NOTE Confidence: 0.942083309090909

00:37:02.730 --> 00:37:04.137 looked into the literature of course lots

NOTE Confidence: 0.942083309090909

00:37:04.137 --> 00:37:05.610 of work's been done in the prefrontal.

NOTE Confidence: 0.942083309090909

00:37:05.610 --> 00:37:07.120 So. So that's that's amazing

NOTE Confidence: 0.942083309090909

00:37:07.120 --> 00:37:08.970 because we could build on that.

NOTE Confidence: 0.942083309090909

00:37:08.970 --> 00:37:10.834 But what we were a little bit surprised

NOTE Confidence: 0.942083309090909

00:37:10.834 --> 00:37:13.047 to find is most times when we read these

NOTE Confidence: 0.942083309090909

00:37:13.047 --> 00:37:15.166 papers but the sort of end point of

NOTE Confidence: 0.942083309090909

00:37:15.166 --> 00:37:17.008 development of the prefrontal was like

NOTE Confidence: 0.942083309090909

00:37:17.008 --> 00:37:19.283 P60 or something and we're like okay,

NOTE Confidence: 0.942083309090909

00:37:19.290 --> 00:37:21.173 is that really the end because it

NOTE Confidence: 0.942083309090909

00:37:21.173 --> 00:37:23.094 seems pretty early to me and Kevin

NOTE Confidence: 0.942083309090909

00:37:23.094 --> 00:37:25.506 and so we started thinking about.

NOTE Confidence: 0.942083309090909

00:37:25.510 --> 00:37:27.030 Expanding this for this window,

NOTE Confidence: 0.942083309090909

00:37:27.030 --> 00:37:29.718 so not just stopping at PP60 you know,

NOTE Confidence: 0.942083309090909

00:37:29.718 --> 00:37:31.510 but to to broaden this out into

NOTE Confidence: 0.942083309090909

00:37:31.569 --> 00:37:33.569 early adulthood and to do it sort of

NOTE Confidence: 0.942083309090909

00:37:33.569 --> 00:37:35.468 go after the second phase of this

NOTE Confidence: 0.942083309090909

00:37:35.470 --> 00:37:37.695 using a combination of approaches

NOTE Confidence: 0.942083309090909

00:37:37.695 --> 00:37:38.585 from electrophysiology,

NOTE Confidence: 0.942083309090909

00:37:38.590 --> 00:37:40.278 slice Physiology and vivo

NOTE Confidence: 0.942083309090909

00:37:40.278 --> 00:37:41.544 Physiology and behavior.

NOTE Confidence: 0.942083309090909

00:37:41.550 --> 00:37:44.134 And as you'll see in a bit overlaying

NOTE Confidence: 0.942083309090909

00:37:44.134 --> 00:37:46.308 things like single cell multi omic

NOTE Confidence: 0.942083309090909

00:37:46.310 --> 00:37:48.935 sort of characterization on top of of

NOTE Confidence: 0.942083309090909

00:37:48.935 --> 00:37:50.990 of the characterization by Physiology.

NOTE Confidence: 0.942083309090909

00:37:50.990 --> 00:37:52.190 We were naive enough to think,

NOTE Confidence: 0.942083309090909

00:37:52.190 --> 00:37:52.435 oh,

NOTE Confidence: 0.942083309090909

00:37:52.435 --> 00:37:53.905 we'll just the first year we'll

NOTE Confidence: 0.942083309090909

00:37:53.905 --> 00:37:54.877 do neurotypical development and

NOTE Confidence: 0.942083309090909

00:37:54.877 --> 00:37:56.041 then we'll just start doing all

NOTE Confidence: 0.942083309090909

00:37:56.041 --> 00:37:57.509 the cool stuff three years later.

NOTE Confidence: 0.942083309090909

00:37:57.509 --> 00:37:58.388 Four years later,

NOTE Confidence: 0.942083309090909

00:37:58.390 --> 00:38:00.265 we're just wrapping up the

NOTE Confidence: 0.942083309090909

00:38:00.265 --> 00:38:01.390 first neurotypical paper.

NOTE Confidence: 0.942083309090909

00:38:01.390 --> 00:38:02.972 But it was required because if you

NOTE Confidence: 0.942083309090909

00:38:02.972 --> 00:38:04.383 don't have robust readouts and

NOTE Confidence: 0.942083309090909

00:38:04.383 --> 00:38:05.747 really understand the development,

NOTE Confidence: 0.942083309090909

00:38:05.750 --> 00:38:06.905 then you don't know what you know,

NOTE Confidence: 0.942083309090909

00:38:06.910 --> 00:38:07.558 what's your readout.

NOTE Confidence: 0.942083309090909

00:38:07.558 --> 00:38:09.070 And I think that was the goal.

NOTE Confidence: 0.942083309090909

00:38:09.070 --> 00:38:11.950 So is the brain done developing at P60?

NOTE Confidence: 0.942083309090909

00:38:11.950 --> 00:38:14.390 How many people think? The answer is yes.

NOTE Confidence: 0.942083309090909

00:38:14.390 --> 00:38:16.900 Oh, good, cause it's not.

NOTE Confidence: 0.942083309090909

00:38:16.900 --> 00:38:17.068 OK,

NOTE Confidence: 0.942083309090909

00:38:17.068 --> 00:38:18.244 So what kinds of now this is

NOTE Confidence: 0.942083309090909

00:38:18.244 --> 00:38:20.208 all new to me because I'm not a

NOTE Confidence: 0.942083309090909

00:38:20.208 --> 00:38:20.734 behavioral neuroscientist.

NOTE Confidence: 0.942083309090909

00:38:20.740 --> 00:38:22.840 So thank God for Kevin and Bernardo's

NOTE Confidence: 0.942083309090909

00:38:22.840 --> 00:38:24.388 lab because they've developed a

NOTE Confidence: 0.942083309090909

00:38:24.388 --> 00:38:26.453 lot of really great tools and and

NOTE Confidence: 0.942083309090909

00:38:26.453 --> 00:38:28.546 behavioral tasks and obviously all

NOTE Confidence: 0.942083309090909

00:38:28.546 --> 00:38:29.854 the electrophysiological readouts.

NOTE Confidence: 0.942083309090909

00:38:29.860 --> 00:38:31.892 So what Kevin decided to do first is

NOTE Confidence: 0.942083309090909

00:38:31.892 --> 00:38:33.700 start with a simple reversal task.

NOTE Confidence: 0.942083309090909

00:38:33.700 --> 00:38:35.478 And so mice were placed in a

NOTE Confidence: 0.942083309090909

00:38:35.478 --> 00:38:36.899 box with three nose port,

NOTE Confidence: 0.942083309090909

00:38:36.900 --> 00:38:39.240 they had to learn to initiate by poking in

NOTE Confidence: 0.942083309090909

00:38:39.240 --> 00:38:41.754 the center and then deciding right or left.

NOTE Confidence: 0.942083309090909

00:38:41.760 --> 00:38:43.280 And over the course of these trial errors,

NOTE Confidence: 0.942083309090909

00:38:43.280 --> 00:38:44.744 they would learn that one side

NOTE Confidence: 0.942083309090909

00:38:44.744 --> 00:38:46.359 is rewarded and the other's not.

NOTE Confidence: 0.942083309090909

00:38:46.360 --> 00:38:47.560 So after 20 tile,

NOTE Confidence: 0.942083309090909

00:38:47.560 --> 00:38:48.160 20 trials,

NOTE Confidence: 0.942083309090909

00:38:48.160 --> 00:38:48.964 then everything's reversed.

NOTE Confidence: 0.942083309090909

00:38:48.964 --> 00:38:50.572 And So what you're going to

NOTE Confidence: 0.942083309090909

00:38:50.572 --> 00:38:51.959 be measuring is switching.

NOTE Confidence: 0.942083309090909

00:38:51.960 --> 00:38:53.720 And we want to know how switching happens.

NOTE Confidence: 0.942083309090909

00:38:53.720 --> 00:38:55.400 That's plasticity and flexibility,

NOTE Confidence: 0.942083309090909

00:38:55.400 --> 00:38:57.500 how that changes with age.

NOTE Confidence: 0.942083309090909

00:38:57.500 --> 00:39:00.328 And what Kevin found is first of

NOTE Confidence: 0.942083309090909

00:39:00.328 --> 00:39:03.236 all just to say that the it's not

NOTE Confidence: 0.942083309090909

00:39:03.236 --> 00:39:04.972 really due to the number of trials.

NOTE Confidence: 0.942083309090909

00:39:04.980 --> 00:39:06.375 So he did a lot of controls on this.

NOTE Confidence: 0.942083309090909

00:39:06.380 --> 00:39:08.558 But what's really cool is in

NOTE Confidence: 0.942083309090909

00:39:08.558 --> 00:39:10.010 assessing the differences between

NOTE Confidence: 0.888517568

00:39:10.078 --> 00:39:12.658 the start and the end of the of the plateau.

NOTE Confidence: 0.888517568

00:39:12.660 --> 00:39:13.724 What he's finding, oops,

NOTE Confidence: 0.888517568

00:39:13.724 --> 00:39:15.416 I got, I clicked too fast,

NOTE Confidence: 0.888517568

00:39:15.416 --> 00:39:17.881 is that the young animals were much better

NOTE Confidence: 0.888517568

00:39:17.881 --> 00:39:20.226 at adapting their behavior than when the

NOTE Confidence: 0.888517568

00:39:20.226 --> 00:39:22.416 rules shifted than the older animals.

NOTE Confidence: 0.888517568

00:39:22.420 --> 00:39:23.414 And when I say young and old,

NOTE Confidence: 0.888517568

00:39:23.420 --> 00:39:26.336 we're talking about between this P60 up to P,

NOTE Confidence: 0.888517568

00:39:26.340 --> 00:39:27.426 right? Like. Okay.

NOTE Confidence: 0.888517568

00:39:27.426 --> 00:39:29.236 So, so there's a big,

NOTE Confidence: 0.888517568

00:39:29.240 --> 00:39:32.184 there's a lot happening up to P120 here,

NOTE Confidence: 0.888517568

00:39:32.184 --> 00:39:33.936 right, and beyond just the simple

NOTE Confidence: 0.888517568

00:39:33.936 --> 00:39:35.261 sort of deterministic reversal

NOTE Confidence: 0.888517568

00:39:35.261 --> 00:39:37.313 task where this is now showing

NOTE Confidence: 0.888517568

00:39:37.313 --> 00:39:39.240 the two ages in blue and red.

NOTE Confidence: 0.888517568

00:39:39.240 --> 00:39:40.160 And that's really, you know,

NOTE Confidence: 0.888517568

00:39:40.160 --> 00:39:41.623 the first important point I just showed

NOTE Confidence: 0.888517568

00:39:41.623 --> 00:39:43.080 you just graphed slightly differently.

NOTE Confidence: 0.888517568

00:39:43.080 --> 00:39:44.512 What's more interesting is

NOTE Confidence: 0.888517568

00:39:44.512 --> 00:39:46.302 when he started bringing in.

NOTE Confidence: 0.888517568

00:39:46.310 --> 00:39:47.660 Probabilistic 2 armed bandit task

NOTE Confidence: 0.888517568

00:39:47.660 --> 00:39:49.657 which is now going to start to

NOTE Confidence: 0.888517568

00:39:49.657 --> 00:39:51.132 get at behavioral strategies the

NOTE Confidence: 0.888517568

00:39:51.132 --> 00:39:52.710 animals use during this process.

NOTE Confidence: 0.888517568

00:39:52.710 --> 00:39:54.447 So the two armed bandit task is a task

NOTE Confidence: 0.888517568

00:39:54.447 --> 00:39:55.977 used by many groups and Bernardo's lab

NOTE Confidence: 0.888517568

00:39:55.977 --> 00:39:58.259 has done a lot on this but never really

NOTE Confidence: 0.888517568

00:39:58.259 --> 00:39:59.629 looked during development and aging.

NOTE Confidence: 0.888517568

00:39:59.630 --> 00:40:01.345 So that's what Kevin wanted to do.

NOTE Confidence: 0.888517568

00:40:01.350 --> 00:40:03.048 And essentially it's it's a different

NOTE Confidence: 0.888517568

00:40:03.048 --> 00:40:04.840 task because you can adjust the

NOTE Confidence: 0.888517568

00:40:04.840 --> 00:40:06.670 probability that each port is rewarded.

NOTE Confidence: 0.888517568

00:40:06.670 --> 00:40:08.598 You can kind of switch between

NOTE Confidence: 0.888517568

00:40:08.598 --> 00:40:10.070 90 and 10 probabilities,

NOTE Confidence: 0.888517568

00:40:10.070 --> 00:40:12.262 high versus low reward and then you can

NOTE Confidence: 0.888517568

00:40:12.262 --> 00:40:14.470 start to introduce sort of this this.

NOTE Confidence: 0.888517568

00:40:14.470 --> 00:40:14.936 You know,

NOTE Confidence: 0.888517568

00:40:14.936 --> 00:40:16.334 you know this sort of variation

NOTE Confidence: 0.888517568

00:40:16.334 --> 00:40:17.981 in the tasks and the animals

NOTE Confidence: 0.888517568

00:40:17.981 --> 00:40:19.386 have to adjust their strategy.

NOTE Confidence: 0.888517568

00:40:19.390 --> 00:40:20.122 It's harder, right?

NOTE Confidence: 0.888517568

00:40:20.122 --> 00:40:22.350 So what does the results show on the right?

NOTE Confidence: 0.888517568

00:40:22.350 --> 00:40:23.614 You can see again,

NOTE Confidence: 0.888517568

00:40:23.614 --> 00:40:25.194 the younger animals are much

NOTE Confidence: 0.888517568

00:40:25.194 --> 00:40:26.934 better at dealing with this

NOTE Confidence: 0.888517568

00:40:26.934 --> 00:40:28.629 and switching versus the older.

NOTE Confidence: 0.888517568

00:40:28.630 --> 00:40:30.580 So they they switch and they

NOTE Confidence: 0.888517568

00:40:30.580 --> 00:40:32.590 they're much more flexible and they

NOTE Confidence: 0.888517568

00:40:32.590 --> 00:40:34.540 switch to the reward report faster.

NOTE Confidence: 0.888517568

00:40:34.540 --> 00:40:35.932 So then the question is what's

NOTE Confidence: 0.888517568

00:40:35.932 --> 00:40:37.818 going on in the brain during this?

NOTE Confidence: 0.888517568

00:40:37.820 --> 00:40:40.480 And so Kevin started to record the

NOTE Confidence: 0.888517568

00:40:40.480 --> 00:40:42.685 activity using fiber photometry using

NOTE Confidence: 0.888517568

00:40:42.685 --> 00:40:45.125 the calcium indicator G Camp 6 and he

NOTE Confidence: 0.888517568

00:40:45.125 --> 00:40:47.580 can record activity during the task.

NOTE Confidence: 0.888517568

00:40:47.580 --> 00:40:49.602 And what's really cool about these

NOTE Confidence: 0.888517568

00:40:49.602 --> 00:40:52.311 experiments is what he found is that nice

NOTE Confidence: 0.888517568

00:40:52.311 --> 00:40:54.620 essentially during the two on bandit task,

NOTE Confidence: 0.888517568

00:40:54.620 --> 00:40:55.367 it turns out,

NOTE Confidence: 0.888517568

00:40:55.367 --> 00:40:57.939 as you can see here that you can actually,

NOTE Confidence: 0.888517568

00:40:57.940 --> 00:40:59.956 you know you can align to the

NOTE Confidence: 0.888517568

00:40:59.956 --> 00:41:01.779 initiation choice and out the outcome.

NOTE Confidence: 0.888517568

00:41:01.780 --> 00:41:03.313 You can see there's a huge difference

NOTE Confidence: 0.888517568

00:41:03.313 --> 00:41:04.842 in the calcium activity during the

NOTE Confidence: 0.888517568

00:41:04.842 --> 00:41:06.498 rewarded but not the unrewarded trials.

NOTE Confidence: 0.888517568

00:41:06.500 --> 00:41:08.000 And interestingly there's

NOTE Confidence: 0.888517568

00:41:08.000 --> 00:41:09.500 major age-related differences.

NOTE Confidence: 0.888517568

00:41:09.500 --> 00:41:11.740 It's actually showing that there's

NOTE Confidence: 0.888517568

00:41:11.740 --> 00:41:12.864 essentially a decrease, right?

NOTE Confidence: 0.888517568

00:41:12.864 --> 00:41:14.550 You can see there's a decrease

NOTE Confidence: 0.888517568

00:41:14.604 --> 00:41:15.874 in activity during the switching

NOTE Confidence: 0.888517568

00:41:15.874 --> 00:41:17.700 which was a little bit unexpected,

NOTE Confidence: 0.888517568

00:41:17.700 --> 00:41:19.254 but actually makes sense with other

NOTE Confidence: 0.888517568

00:41:19.254 --> 00:41:20.898 data that you'll see in a second.

NOTE Confidence: 0.888517568

00:41:20.900 --> 00:41:22.900 So there's age-related differences

NOTE Confidence: 0.888517568

00:41:22.900 --> 00:41:24.400 in terms of.

NOTE Confidence: 0.888517568

00:41:24.400 --> 00:41:26.458 Of of of how the activity patterns

NOTE Confidence: 0.888517568

00:41:26.458 --> 00:41:28.419 are aligning with these behavioral

NOTE Confidence: 0.888517568

00:41:28.419 --> 00:41:29.437 switching behavior.

NOTE Confidence: 0.888517568

00:41:29.440 --> 00:41:29.656 So.

NOTE Confidence: 0.888517568

00:41:29.656 --> 00:41:30.952 So now the question is what's

NOTE Confidence: 0.888517568

00:41:30.952 --> 00:41:32.392 happening at the circuit level and

NOTE Confidence: 0.888517568

00:41:32.392 --> 00:41:33.874 this is where slice Physiology comes

NOTE Confidence: 0.888517568

00:41:33.874 --> 00:41:35.638 in and he's been doing a lot on this.

NOTE Confidence: 0.888517568

00:41:35.640 --> 00:41:36.918 I'm only going to highlight the

NOTE Confidence: 0.888517568

00:41:36.918 --> 00:41:37.557 key results here.

NOTE Confidence: 0.888517568

00:41:37.560 --> 00:41:39.317 He's been looking at the input changes,

NOTE Confidence: 0.86784627

00:41:39.320 --> 00:41:41.510 sort of looking at refinement and

NOTE Confidence: 0.86784627

00:41:41.510 --> 00:41:43.348 connectivity, also local local circuit

NOTE Confidence: 0.86784627

00:41:43.348 --> 00:41:45.998 changes in the in the different ages

NOTE Confidence: 0.86784627

00:41:45.998 --> 00:41:48.658 and what he found by doing slice

NOTE Confidence: 0.86784627

00:41:48.658 --> 00:41:50.930 electrophysiology in the prefrontal cortex.

NOTE Confidence: 0.86784627

00:41:50.930 --> 00:41:53.486 Is in in the punchline of this given the

NOTE Confidence: 0.86784627

00:41:53.486 --> 00:41:55.676 interest of time is it's a systematic

NOTE Confidence: 0.86784627

00:41:55.676 --> 00:41:57.610 shift from excitation to inhibition,

NOTE Confidence: 0.86784627

00:41:57.610 --> 00:42:00.490 they become more inhibition dominant during

NOTE Confidence: 0.86784627

00:42:00.490 --> 00:42:03.530 this window of P60P90 to 120 exactly when

NOTE Confidence: 0.86784627

00:42:03.530 --> 00:42:05.337 we're seeing the behavioral changes, right.

NOTE Confidence: 0.86784627

00:42:05.337 --> 00:42:07.200 So you can see in the in on the

NOTE Confidence: 0.86784627

00:42:07.259 --> 00:42:09.170 bottom the way the data is graphed,

NOTE Confidence: 0.86784627

00:42:09.170 --> 00:42:12.090 he plots E / e E plus I.

NOTE Confidence: 0.86784627

00:42:12.090 --> 00:42:13.810 It's really enabling us to look at the,

NOTE Confidence: 0.86784627

00:42:13.810 --> 00:42:15.875 the, the inputs that are more excitation

NOTE Confidence: 0.86784627

00:42:15.875 --> 00:42:17.210 dominant versus inhibition dominant.

NOTE Confidence: 0.86784627

00:42:17.210 --> 00:42:19.698 Hopefully we could see as this big shift.

NOTE Confidence: 0.86784627

00:42:19.700 --> 00:42:19.980 Right.

NOTE Confidence: 0.86784627

00:42:19.980 --> 00:42:22.500 And so this is a lot of slice Physiology

NOTE Confidence: 0.86784627

00:42:22.568 --> 00:42:24.656 is down over many different animals

NOTE Confidence: 0.86784627

00:42:24.660 --> 00:42:26.478 and then he can go on and and do

NOTE Confidence: 0.86784627

00:42:26.478 --> 00:42:28.153 more because he can then start to

NOTE Confidence: 0.86784627

00:42:28.153 --> 00:42:30.158 look at the PV inner neurons and

NOTE Confidence: 0.86784627

00:42:30.158 --> 00:42:31.828 using viral strategies where you

NOTE Confidence: 0.86784627

00:42:31.828 --> 00:42:34.060 can target and label the PV cells,

NOTE Confidence: 0.86784627

00:42:34.060 --> 00:42:36.034 he could then also record from the

NOTE Confidence: 0.86784627

00:42:36.034 --> 00:42:37.698 PV neurons during the same task.

NOTE Confidence: 0.86784627

00:42:37.700 --> 00:42:39.300 And what's cool about that?

NOTE Confidence: 0.86784627

00:42:39.300 --> 00:42:41.055 This is just some of the the viral tools

NOTE Confidence: 0.86784627

00:42:41.055 --> 00:42:42.950 we can use in mice and marmosets that

NOTE Confidence: 0.86784627

00:42:42.950 --> 00:42:44.984 were developed by by Gord for Shell's

NOTE Confidence: 0.86784627

00:42:44.984 --> 00:42:47.268 group and others and Ben Deverman's lab.

NOTE Confidence: 0.86784627

00:42:47.268 --> 00:42:49.847 We can essentially he could find the opposite

NOTE Confidence: 0.86784627

00:42:49.847 --> 00:42:52.600 in terms of activity changes in the PV cells.

NOTE Confidence: 0.86784627

00:42:52.600 --> 00:42:55.120 So in the excitatory neurons when he recorded

NOTE Confidence: 0.86784627

00:42:55.120 --> 00:42:57.557 from those right it's a shift from E to I,

NOTE Confidence: 0.86784627

00:42:57.560 --> 00:42:59.352 but in the PV cells they shift

NOTE Confidence: 0.86784627

00:42:59.352 --> 00:43:01.159 up right so is the opposite.

NOTE Confidence: 0.86784627

00:43:01.160 --> 00:43:02.576 So it's really cool and so it now

NOTE Confidence: 0.86784627

00:43:02.576 --> 00:43:04.230 it all makes sense but at the time

NOTE Confidence: 0.86784627

00:43:04.230 --> 00:43:05.560 we didn't we didn't know this.

NOTE Confidence: 0.86784627

00:43:05.560 --> 00:43:07.126 So now this is really suggesting

NOTE Confidence: 0.86784627

00:43:07.126 --> 00:43:08.571 that the shift from excitation

NOTE Confidence: 0.86784627

00:43:08.571 --> 00:43:10.326 inhibition might be underlying the

NOTE Confidence: 0.86784627

00:43:10.326 --> 00:43:12.268 behavioral shift that he saw with

NOTE Confidence: 0.86784627

00:43:12.268 --> 00:43:14.254 the two armed bandit and in very,

NOTE Confidence: 0.86784627

00:43:14.254 --> 00:43:16.282 very like very new data now.

NOTE Confidence: 0.86784627

00:43:16.290 --> 00:43:17.815 He's starting to test that

NOTE Confidence: 0.86784627

00:43:17.815 --> 00:43:18.730 hypothesis more directly.

NOTE Confidence: 0.86784627

00:43:18.730 --> 00:43:20.404 So the real killer experiment then

NOTE Confidence: 0.86784627

00:43:20.404 --> 00:43:22.188 is to block inhibition in the older

NOTE Confidence: 0.86784627

00:43:22.188 --> 00:43:23.623 mice and see if you can shift

NOTE Confidence: 0.86784627

00:43:23.681 --> 00:43:25.247 them back to becoming a younger,

NOTE Confidence: 0.86784627

00:43:25.250 --> 00:43:27.730 more plastic, more flexible mouse.

NOTE Confidence: 0.86784627

00:43:27.730 --> 00:43:28.714 That could be interesting.

NOTE Confidence: 0.86784627

00:43:28.714 --> 00:43:29.944 So we did that experiment

NOTE Confidence: 0.86784627

00:43:29.944 --> 00:43:31.206 and this is very new data.

NOTE Confidence: 0.86784627

00:43:31.210 --> 00:43:33.088 So basically he used the dreads,

NOTE Confidence: 0.86784627

00:43:33.090 --> 00:43:35.204 the chemogenetic way to do with this.

NOTE Confidence: 0.86784627

00:43:35.210 --> 00:43:37.250 So if you inhibit the PV

NOTE Confidence: 0.86784627

00:43:37.250 --> 00:43:38.270 activity using dreads.

NOTE Confidence: 0.86784627

00:43:38.270 --> 00:43:39.760 The older animals P120 were

NOTE Confidence: 0.86784627

00:43:39.760 --> 00:43:41.710 trained on the two armed bandit.

NOTE Confidence: 0.86784627

00:43:41.710 --> 00:43:43.628 All the animals received the drug treatment,

NOTE Confidence: 0.86784627

00:43:43.630 --> 00:43:45.124 half had M cherry and orange

NOTE Confidence: 0.86784627

00:43:45.124 --> 00:43:46.761 and the other had the inhibitory

NOTE Confidence: 0.86784627

00:43:46.761 --> 00:43:48.784 dread and the PV neurons in blue.

NOTE Confidence: 0.86784627

00:43:48.790 --> 00:43:51.100 And he found that upon acquiring the

NOTE Confidence: 0.86784627

00:43:51.100 --> 00:43:53.409 two armed bandit task the adult mice.

NOTE Confidence: 0.86784627

00:43:53.410 --> 00:43:54.706 With less inhibition performed

NOTE Confidence: 0.86784627

00:43:54.706 --> 00:43:56.650 better than the control as shown

NOTE Confidence: 0.86784627

00:43:56.710 --> 00:43:58.050 by their increased reward.

NOTE Confidence: 0.86784627

00:43:58.050 --> 00:43:59.694 So they essentially the animals are

NOTE Confidence: 0.86784627

00:43:59.694 --> 00:44:01.290 better at tracking reward over time.

NOTE Confidence: 0.86784627

00:44:01.290 --> 00:44:02.346 And then, you know,

NOTE Confidence: 0.86784627

00:44:02.346 --> 00:44:04.200 the same animals were then placed on

NOTE Confidence: 0.86784627

00:44:04.200 --> 00:44:05.928 saline and SEM CNO and this is cool,

NOTE Confidence: 0.86784627

00:44:05.930 --> 00:44:08.126 the effect went away so you can reverse it.

NOTE Confidence: 0.931448125

00:44:08.130 --> 00:44:09.370 So there's a lot more to do here.

NOTE Confidence: 0.931448125

00:44:09.370 --> 00:44:11.450 But the data suggesting the

NOTE Confidence: 0.931448125

00:44:11.450 --> 00:44:13.340 inhibition of PV network improves

NOTE Confidence: 0.931448125

00:44:13.340 --> 00:44:15.230 performance in the older mice.

NOTE Confidence: 0.931448125

00:44:15.230 --> 00:44:16.830 Now, there's a lot more to do here

NOTE Confidence: 0.931448125

00:44:16.830 --> 00:44:18.349 in terms of asking how how long,

NOTE Confidence: 0.931448125

00:44:18.350 --> 00:44:20.350 how old you are to switch him back.

NOTE Confidence: 0.931448125

00:44:20.350 --> 00:44:22.142 But I think this is pretty cool because

NOTE Confidence: 0.931448125

00:44:22.142 --> 00:44:23.709 he's doing it in a very select way.

NOTE Confidence: 0.931448125

00:44:23.710 --> 00:44:24.510 And now of course,

NOTE Confidence: 0.931448125

00:44:24.510 --> 00:44:26.252 we're broadening out even more to say, well,

NOTE Confidence: 0.931448125

00:44:26.252 --> 00:44:28.304 what else is happening mechanistically here,

NOTE Confidence: 0.931448125

00:44:28.310 --> 00:44:31.030 not just in mice but also in marmosets?

NOTE Confidence: 0.931448125

00:44:31.030 --> 00:44:32.580 Because we're basically Kevin's training

NOTE Confidence: 0.931448125

00:44:32.580 --> 00:44:34.669 the marmosets to do the same task.

NOTE Confidence: 0.931448125

00:44:34.670 --> 00:44:36.170 So we can track marmosets

NOTE Confidence: 0.931448125

00:44:36.170 --> 00:44:38.110 from six months to two years,

NOTE Confidence: 0.931448125

00:44:38.110 --> 00:44:38.890 and he's already taught them

NOTE Confidence: 0.931448125

00:44:38.890 --> 00:44:40.150 how to do the two armed bandit.

NOTE Confidence: 0.931448125

00:44:40.150 --> 00:44:41.402 They learn really well.

NOTE Confidence: 0.931448125

00:44:41.402 --> 00:44:43.280 And we're also starting to take

NOTE Confidence: 0.931448125

00:44:43.338 --> 00:44:45.156 the brains of mice and marmoset.

NOTE Confidence: 0.931448125

00:44:45.160 --> 00:44:47.232 And start to look in a more unbiased

NOTE Confidence: 0.931448125

00:44:47.232 --> 00:44:49.042 way using on the genetics using

NOTE Confidence: 0.931448125

00:44:49.042 --> 00:44:50.896 cellular and single cell and Moxy

NOTE Confidence: 0.931448125

00:44:50.959 --> 00:44:52.783 omics to look at which synapses

NOTE Confidence: 0.931448125

00:44:52.783 --> 00:44:54.432 and cells are changing over time.

NOTE Confidence: 0.931448125

00:44:54.432 --> 00:44:56.160 And again I just showed you some of

NOTE Confidence: 0.931448125

00:44:56.207 --> 00:44:57.587 the behavior and and the Physiology

NOTE Confidence: 0.931448125

00:44:57.587 --> 00:44:59.398 to try to zip all this together.

NOTE Confidence: 0.931448125

00:44:59.400 --> 00:45:00.728 But the hope is at the end of

NOTE Confidence: 0.931448125

00:45:00.728 --> 00:45:02.064 the day probably many years from

NOTE Confidence: 0.931448125

00:45:02.064 --> 00:45:03.680 now when all this data comes in,

NOTE Confidence: 0.931448125

00:45:03.680 --> 00:45:05.776 it might give us more of a mechanistic

NOTE Confidence: 0.931448125

00:45:05.776 --> 00:45:07.719 handle on which cells are changing,

NOTE Confidence: 0.931448125

00:45:07.720 --> 00:45:10.506 which circuits are changing and then how

NOTE Confidence: 0.931448125

00:45:10.506 --> 00:45:12.760 those mechanisms relate to the behavior.

NOTE Confidence: 0.931448125

00:45:12.760 --> 00:45:14.184 And just to say real quick you know

NOTE Confidence: 0.931448125

00:45:14.184 --> 00:45:15.770 the single cell is starting to come

NOTE Confidence: 0.931448125

00:45:15.770 --> 00:45:16.718 out super interesting already.

NOTE Confidence: 0.931448125

00:45:16.720 --> 00:45:18.035 It's starting to highlight cell

NOTE Confidence: 0.931448125

00:45:18.035 --> 00:45:19.666 types like astrocytes and all the

NOTE Confidence: 0.931448125

00:45:19.666 --> 00:45:20.996 dendrocytes which is pretty cool.

NOTE Confidence: 0.931448125

00:45:21.000 --> 00:45:23.051 So it's pretty early days I was

NOTE Confidence: 0.931448125

00:45:23.051 --> 00:45:24.294 mentioning these marmosets if

NOTE Confidence: 0.931448125

00:45:24.294 --> 00:45:26.142 you've never seen a marmoset they're

NOTE Confidence: 0.931448125

00:45:26.142 --> 00:45:27.629 they're really pretty cool they

NOTE Confidence: 0.931448125

00:45:27.629 --> 00:45:29.400 can actually learn to do this task.

NOTE Confidence: 0.931448125

00:45:29.400 --> 00:45:30.895 They can touch the touchscreen

NOTE Confidence: 0.931448125

00:45:30.895 --> 00:45:32.949 instead of licking like a mouse they

NOTE Confidence: 0.931448125

00:45:32.949 --> 00:45:34.706 can Kevin's trained them how to how

NOTE Confidence: 0.931448125

00:45:34.706 --> 00:45:36.879 to do this sort of sort of reversal

NOTE Confidence: 0.931448125

00:45:36.879 --> 00:45:39.620 learning and and to to on bandit task.

NOTE Confidence: 0.931448125

00:45:39.620 --> 00:45:41.124 They do quite well.

NOTE Confidence: 0.931448125

00:45:41.124 --> 00:45:41.500 They,

NOTE Confidence: 0.931448125

00:45:41.500 --> 00:45:43.327 they they like to do the task and so

NOTE Confidence: 0.931448125

00:45:43.327 --> 00:45:44.980 stay tuned for some of this data.

NOTE Confidence: 0.931448125

00:45:44.980 --> 00:45:47.260 But already he's starting to show

NOTE Confidence: 0.931448125

00:45:47.260 --> 00:45:48.976 in parallel some of these animals

NOTE Confidence: 0.931448125

00:45:48.976 --> 00:45:51.033 were starting to be able to then do

NOTE Confidence: 0.931448125

00:45:51.033 --> 00:45:52.677 some of the work knowing what we

NOTE Confidence: 0.931448125

00:45:52.677 --> 00:45:54.490 know in mouse and applying this to

NOTE Confidence: 0.931448125

00:45:54.543 --> 00:45:56.195 the to the marmosets and and and

NOTE Confidence: 0.931448125

00:45:56.195 --> 00:45:57.630 ultimately this is sort of a summary

NOTE Confidence: 0.931448125

00:45:57.680 --> 00:45:58.580 of where we're going.

NOTE Confidence: 0.931448125

00:45:58.580 --> 00:46:01.332 We can start to also look at anatomical

NOTE Confidence: 0.931448125

00:46:01.332 --> 00:46:02.020 tracing experiments.

NOTE Confidence: 0.931448125

00:46:02.020 --> 00:46:06.150 And we can also start to then manipulate C4C,

NOTE Confidence: 0.931448125

00:46:06.150 --> 00:46:06.650 SM D1,

NOTE Confidence: 0.931448125

00:46:06.650 --> 00:46:08.400 some of the schema mutants like Rin

NOTE Confidence: 0.931448125

00:46:08.460 --> 00:46:10.484 2A and then we can then pair that

NOTE Confidence: 0.931448125

00:46:10.484 --> 00:46:11.336 with environmental challenges.

NOTE Confidence: 0.931448125

00:46:11.340 --> 00:46:13.314 So first we look at genetics and

NOTE Confidence: 0.931448125

00:46:13.314 --> 00:46:15.060 see what these genetic leads,

NOTE Confidence: 0.931448125

00:46:15.060 --> 00:46:15.424 knockouts,

NOTE Confidence: 0.931448125

00:46:15.424 --> 00:46:17.608 wild types are doing to circuits

NOTE Confidence: 0.931448125

00:46:17.608 --> 00:46:18.336 and behavior.

NOTE Confidence: 0.931448125

00:46:18.340 --> 00:46:19.432 And then we can,

NOTE Confidence: 0.931448125

00:46:19.432 --> 00:46:21.070 based on the adolescent period do

NOTE Confidence: 0.931448125

00:46:21.134 --> 00:46:23.472 a second hit and see how environmental

NOTE Confidence: 0.931448125

00:46:23.472 --> 00:46:24.900 challenges like social isolation

NOTE Confidence: 0.931448125

00:46:24.900 --> 00:46:26.007 or social stress.

NOTE Confidence: 0.931448125

00:46:26.010 --> 00:46:27.685 Pairs with and combines with

NOTE Confidence: 0.931448125

00:46:27.685 --> 00:46:29.360 these genetic challenges and how

NOTE Confidence: 0.950317113181818

00:46:29.415 --> 00:46:31.257 ultimately that leads to changes in

NOTE Confidence: 0.950317113181818

00:46:31.257 --> 00:46:33.370 these behaviors as a starting point.

NOTE Confidence: 0.950317113181818

00:46:33.370 --> 00:46:35.323 And so we hope ultimately that at

NOTE Confidence: 0.950317113181818

00:46:35.323 --> 00:46:37.888 the end you might learn more and in

NOTE Confidence: 0.950317113181818

00:46:37.888 --> 00:46:39.770 more systematic way as we get more

NOTE Confidence: 0.950317113181818

00:46:39.770 --> 00:46:41.090 on the genetics and the biology,

NOTE Confidence: 0.950317113181818

00:46:41.090 --> 00:46:42.954 we we we can then apply what we

NOTE Confidence: 0.950317113181818

00:46:42.954 --> 00:46:45.328 learn to these other sort of circuit

NOTE Confidence: 0.950317113181818

00:46:45.328 --> 00:46:46.804 and cognitive level readouts.

NOTE Confidence: 0.950317113181818

00:46:46.810 --> 00:46:48.406 And then ultimately the goal is,

NOTE Confidence: 0.950317113181818

00:46:48.410 --> 00:46:50.024 Marina said in her introduction is

NOTE Confidence: 0.950317113181818

00:46:50.024 --> 00:46:51.866 to try to translate some of this

NOTE Confidence: 0.950317113181818

00:46:51.866 --> 00:46:53.539 work to the clinic to the patients.

NOTE Confidence: 0.950317113181818

00:46:53.540 --> 00:46:55.040 And and one example,

NOTE Confidence: 0.950317113181818

00:46:55.040 --> 00:46:57.819 C4 happens to be secreted and it has

NOTE Confidence: 0.950317113181818

00:46:57.820 --> 00:46:59.212 come out in CSF and we can measure

NOTE Confidence: 0.950317113181818

00:46:59.212 --> 00:47:00.717 it and Steve Mccarroll has done that

NOTE Confidence: 0.950317113181818

00:47:00.717 --> 00:47:02.300 and some of that works published.

NOTE Confidence: 0.950317113181818

00:47:02.300 --> 00:47:04.106 C4 can be not only read out

NOTE Confidence: 0.950317113181818

00:47:04.106 --> 00:47:05.739 and relates to copy numbers.

NOTE Confidence: 0.950317113181818

00:47:05.740 --> 00:47:07.735 So that's a good proof of concept,

NOTE Confidence: 0.950317113181818

00:47:07.740 --> 00:47:09.504 but we can read out other molecules

NOTE Confidence: 0.950317113181818

00:47:09.504 --> 00:47:11.194 that we're studying in the context

NOTE Confidence: 0.950317113181818

00:47:11.194 --> 00:47:12.659 of other disorders like Alzheimer's,

NOTE Confidence: 0.950317113181818

00:47:12.660 --> 00:47:14.820 a lot of neuroimmune molecules and

NOTE Confidence: 0.950317113181818

00:47:14.820 --> 00:47:17.406 synaptic markers we can read out in CSF.

NOTE Confidence: 0.950317113181818

00:47:17.410 --> 00:47:19.078 And thanks to a really amazing

NOTE Confidence: 0.950317113181818

00:47:19.078 --> 00:47:20.874 collaborative effort by many here that

NOTE Confidence: 0.950317113181818

00:47:20.874 --> 00:47:22.770 are also involved in the schizophrenia

NOTE Confidence: 0.950317113181818

00:47:22.770 --> 00:47:23.970 Spectrum biomarker consortium.

NOTE Confidence: 0.950317113181818

00:47:23.970 --> 00:47:25.524 The idea is what if we could

NOTE Confidence: 0.950317113181818

00:47:25.524 --> 00:47:27.063 start to bank and collect CSF

NOTE Confidence: 0.950317113181818

00:47:27.063 --> 00:47:28.689 not just from the later stage,

NOTE Confidence: 0.950317113181818

00:47:28.690 --> 00:47:30.342 but from this early stage of individuals

NOTE Confidence: 0.950317113181818

00:47:30.342 --> 00:47:32.250 that are at risk for developing

NOTE Confidence: 0.950317113181818

00:47:32.250 --> 00:47:33.405 schizophrenia or schizophrenia,

NOTE Confidence: 0.950317113181818

00:47:33.410 --> 00:47:34.946 bipolar and control and start to

NOTE Confidence: 0.950317113181818

00:47:34.946 --> 00:47:36.537 measure some of the leads that

NOTE Confidence: 0.950317113181818

00:47:36.537 --> 00:47:38.085 are coming out of the genetics.

NOTE Confidence: 0.950317113181818

00:47:38.090 --> 00:47:39.644 And then that would hopefully enable

NOTE Confidence: 0.950317113181818

00:47:39.644 --> 00:47:41.649 us to start to stratify patients.

NOTE Confidence: 0.950317113181818

00:47:41.650 --> 00:47:43.006 And as we get more information,

NOTE Confidence: 0.950317113181818

00:47:43.010 --> 00:47:44.690 we'll have better ways of reading

NOTE Confidence: 0.950317113181818

00:47:44.690 --> 00:47:45.873 out these different markers

NOTE Confidence: 0.950317113181818

00:47:45.873 --> 00:47:47.378 in the samples of patients.

NOTE Confidence: 0.950317113181818

00:47:47.380 --> 00:47:49.390 And relate this to the biology

NOTE Confidence: 0.950317113181818

00:47:49.390 --> 00:47:51.460 and ultimately to to cognition.

NOTE Confidence: 0.950317113181818

00:47:51.460 --> 00:47:53.596 So longterm goal that I think C4 is

NOTE Confidence: 0.950317113181818

00:47:53.596 --> 00:47:55.857 a good example of a genetic lead.

NOTE Confidence: 0.950317113181818

00:47:55.860 --> 00:47:57.869 We understand a little bit about the

NOTE Confidence: 0.950317113181818

00:47:57.869 --> 00:48:00.269 biology and we can in fact read out it

NOTE Confidence: 0.950317113181818

00:48:00.269 --> 00:48:02.173 on the genetic level and in the CSF

NOTE Confidence: 0.950317113181818

00:48:02.173 --> 00:48:04.096 and and I think this is the first start,

NOTE Confidence: 0.950317113181818

00:48:04.096 --> 00:48:06.179 but I think we have a long ways to go.

NOTE Confidence: 0.950317113181818

00:48:06.180 --> 00:48:08.097 But it really is going to require a village,

NOTE Confidence: 0.950317113181818

00:48:08.100 --> 00:48:10.020 a lot of collaboration and a lot of

NOTE Confidence: 0.950317113181818

00:48:10.020 --> 00:48:11.706 feedback from folks like you to think

NOTE Confidence: 0.950317113181818

00:48:11.706 --> 00:48:13.414 about how we could then you know

NOTE Confidence: 0.950317113181818

00:48:13.414 --> 00:48:15.164 expand some of this work into other

NOTE Confidence: 0.950317113181818

00:48:15.164 --> 00:48:17.000 models or into other disease areas.

NOTE Confidence: 0.950317113181818

00:48:17.000 --> 00:48:17.892 I focused on schizophrenia,

NOTE Confidence: 0.950317113181818

00:48:17.892 --> 00:48:19.520 but I think this is highly relevant

NOTE Confidence: 0.950317113181818

00:48:19.520 --> 00:48:20.755 to other disorders as well.

NOTE Confidence: 0.950317113181818

00:48:20.760 --> 00:48:22.769 So I'll end by thanking an amazing

NOTE Confidence: 0.950317113181818

00:48:22.769 --> 00:48:24.211 group of collaborators and support

NOTE Confidence: 0.950317113181818

00:48:24.211 --> 00:48:25.795 the human microglia in my lab.

NOTE Confidence: 0.950317113181818

00:48:25.800 --> 00:48:27.171 They're pretty cool.

NOTE Confidence: 0.950317113181818

00:48:27.171 --> 00:48:28.999 I'm the nucleus there,

NOTE Confidence: 0.950317113181818

00:48:29.000 --> 00:48:30.274 and this is the rest of them.

NOTE Confidence: 0.950317113181818

00:48:30.280 --> 00:48:31.880 Be being goofy at one of our retreats.

NOTE Confidence: 0.950317113181818

00:48:31.880 --> 00:48:34.000 So thanks very much.