WEBVTT

NOTE duration:"01:10:08.1920000"

NOTE language:en-us

NOTE Confidence: 0.8170251

00:00:00.000 --> 00:00:02.340 Doctor Crystal couldn't be here today,

NOTE Confidence: 0.8170251

00:00:02.340 --> 00:00:04.590 so he's asked me to introduce

NOTE Confidence: 0.8170251

00:00:04.590 --> 00:00:06.090 our guest speaker today,

NOTE Confidence: 0.8170251

00:00:06.090 --> 00:00:07.975 Doctor Michael Higley Doctor Higley

NOTE Confidence: 0.8170251

00:00:07.975 --> 00:00:09.860 is currently an associate professor

NOTE Confidence: 0.8170251

00:00:09.914 --> 00:00:11.719 in the Department of Neuroscience.

NOTE Confidence: 0.8170251

00:00:11.720 --> 00:00:14.296 He got his MD and his PhD at

NOTE Confidence: 0.8170251

00:00:14.296 --> 00:00:16.220 the University of Pennsylvania,

NOTE Confidence: 0.8170251

00:00:16.220 --> 00:00:18.604 and then he went on to do his

NOTE Confidence: 0.8170251

00:00:18.604 --> 00:00:20.336 postdoctoral work at Harvard with

NOTE Confidence: 0.8170251

00:00:20.336 --> 00:00:22.466 Bernardo Sabatini where he worked on

NOTE Confidence: 0.8170251

00:00:22.466 --> 00:00:24.722 the basal ganglia and particularly

NOTE Confidence: 0.8170251

00:00:24.722 --> 00:00:27.464 synaptic mechanisms in the basal ganglia.

NOTE Confidence: 0.8170251

00:00:27.470 --> 00:00:31.016 He's gone on in his work here at Yale.

1

NOTE Confidence: 0.8170251

00:00:31.020 --> 00:00:33.652 To continue his efforts to do very

NOTE Confidence: 0.8170251

00:00:33.652 --> 00:00:35.585 basic neuroscience at the synaptic

NOTE Confidence: 0.8170251

00:00:35.585 --> 00:00:37.799 and cellular level and to extend

NOTE Confidence: 0.8170251

00:00:37.799 --> 00:00:39.993 that work to understanding circuits

NOTE Confidence: 0.8170251

00:00:39.993 --> 00:00:42.765 that are relevant for brain disease,

NOTE Confidence: 0.8170251

00:00:42.770 --> 00:00:44.795 whether it be psychiatric illness

NOTE Confidence: 0.8170251

00:00:44.795 --> 00:00:46.010 or neurological illness.

NOTE Confidence: 0.8170251

00:00:46.010 --> 00:00:48.778 And he's going to talk to us today

NOTE Confidence: 0.8170251

00:00:48.778 --> 00:00:51.678 about his work on multiscale imaging,

NOTE Confidence: 0.8170251

00:00:51.680 --> 00:00:54.508 and in this case it's not fMRI,

NOTE Confidence: 0.8170251

00:00:54.510 --> 00:00:56.510 its cellular and circuit level

NOTE Confidence: 0.8170251

00:00:56.510 --> 00:00:59.724 image Ng and he's going to lead us

NOTE Confidence: 0.8170251

00:00:59.724 --> 00:01:01.992 through what some of the current

NOTE Confidence: 0.8170251

00:01:01.992 --> 00:01:03.929 cutting edge techniques are.

NOTE Confidence: 0.8170251

00:01:03.930 --> 00:01:06.555 In preclinical science to reveal

NOTE Confidence: 0.8170251

00:01:06.555 --> 00:01:08.655 links between neuronal networks,

NOTE Confidence: 0.8170251

00:01:08.660 --> 00:01:10.010 behavior and disease.

NOTE Confidence: 0.8170251

00:01:10.010 --> 00:01:11.810 Mike, go for it.

NOTE Confidence: 0.85592675

00:01:13.690 --> 00:01:15.484 Marina, thank you and thanks to

NOTE Confidence: 0.85592675

00:01:15.484 --> 00:01:17.589 all of you for coming today.

NOTE Confidence: 0.85592675

00:01:17.590 --> 00:01:19.522 It's it's an incredible privilege and

NOTE Confidence: 0.85592675

00:01:19.522 --> 00:01:21.494 a pleasure to be here, especially

NOTE Confidence: 0.85592675

00:01:21.494 --> 00:01:23.438 giving talks to two local communities.

NOTE Confidence: 0.85592675

00:01:23.440 --> 00:01:26.360 One of the things that I would I would more

NOTE Confidence: 0.85592675

00:01:26.433 --> 00:01:29.289 than than welcome is both during the talk.

NOTE Confidence: 0.85592675

00:01:29.290 --> 00:01:30.925 If people have questions just

NOTE Confidence: 0.85592675

00:01:30.925 --> 00:01:33.190 just jump right in and ask them.

NOTE Confidence: 0.85592675

00:01:33.190 --> 00:01:35.110 And certainly afterwards if anybody wants

NOTE Confidence: 0.85592675

00:01:35.110 --> 00:01:37.419 to follow up with anything you know,

NOTE Confidence: 0.85592675

00:01:37.420 --> 00:01:39.348 an enormous part of these kinds of talks

NOTE Confidence: 0.85592675

00:01:39.348 --> 00:01:41.263 is to potentially ferment collaborations

NOTE Confidence: 0.85592675

00:01:41.263 --> 00:01:43.558 and an future interactions between.

NOTE Confidence: 0.85592675

00:01:43.560 --> 00:01:44.820 All of us here,

NOTE Confidence: 0.85592675

00:01:44.820 --> 00:01:47.200 at both the preclinical and clinical levels.

NOTE Confidence: 0.85592675

00:01:47.200 --> 00:01:49.848 So happy to keep talking afterwards as well.

NOTE Confidence: 0.85592675

00:01:49.850 --> 00:01:51.500 So today as Marina said,

NOTE Confidence: 0.85592675

00:01:51.500 --> 00:01:53.966 what I'm going to try to give you a

NOTE Confidence: 0.85592675

00:01:53.966 --> 00:01:56.511 sense of is some of the methodological

NOTE Confidence: 0.85592675

00:01:56.511 --> 00:01:58.790 approaches that my lab and others,

NOTE Confidence: 0.85592675

00:01:58.790 --> 00:02:01.016 both here at Yale and another locations

NOTE Confidence: 0.85592675

00:02:01.016 --> 00:02:03.419 have been using to study brain function,

NOTE Confidence: 0.85592675

00:02:03.420 --> 00:02:05.406 its relationship in Part 2 to

NOTE Confidence: 0.85592675

00:02:05.406 --> 00:02:06.399 North psychiatric disorders.

NOTE Confidence: 0.85592675

00:02:06.400 --> 00:02:09.388 So I'm not going to give you like an

NOTE Confidence: 0.85592675

00:02:09.388 --> 00:02:11.700 incredible deep dive in any one story,

NOTE Confidence: 0.85592675

00:02:11.700 --> 00:02:13.818 and in fact I'm going to.

NOTE Confidence: 0.85592675

00:02:13.820 --> 00:02:15.654 Tell you a few stories or parts

NOTE Confidence: 0.85592675

00:02:15.654 --> 00:02:17.030 of a few stories,

NOTE Confidence: 0.85592675

00:02:17.030 --> 00:02:18.776 especially in service to that introduction.

NOTE Confidence: 0.85592675

00:02:18.780 --> 00:02:20.537 Most of what I'm going to tell

NOTE Confidence: 0.85592675

00:02:20.537 --> 00:02:22.000 you is actually unpublished,

NOTE Confidence: 0.85592675

00:02:22.000 --> 00:02:24.838 and in fact a little bit of it at the end

NOTE Confidence: 0.85592675

00:02:24.838 --> 00:02:27.246 is going to be even quite preliminary.

NOTE Confidence: 0.85592675

00:02:27.250 --> 00:02:28.124 But again,

NOTE Confidence: 0.85592675

00:02:28.124 --> 00:02:30.309 hopefully it'll be an interesting

NOTE Confidence: 0.85592675

00:02:30.309 --> 00:02:32.306 and exciting opportunity to sort

NOTE Confidence: 0.85592675

00:02:32.306 --> 00:02:34.160 of learn what we've been doing.

NOTE Confidence: 0.85592675

00:02:34.160 --> 00:02:34.437 OK,

NOTE Confidence: 0.85592675

00:02:34.437 --> 00:02:36.653 so this is a bit of an outline

NOTE Confidence: 0.85592675

00:02:36.653 --> 00:02:38.599 about what I'd like to cover,

NOTE Confidence: 0.85592675

00:02:38.600 --> 00:02:40.913 so first I'm going to tell you a little

NOTE Confidence: 0.85592675

00:02:40.913 --> 00:02:43.629 bit about what behavioral state means to us.

NOTE Confidence: 0.85592675

00:02:43.630 --> 00:02:45.618 Then I'm going to go in for

NOTE Confidence: 0.85592675

00:02:45.618 --> 00:02:47.478 awhile about some of the methods,

NOTE Confidence: 0.85592675

00:02:47.480 --> 00:02:49.388 especially at the imaging the fluorescence

NOTE Confidence: 0.85592675

00:02:49.388 --> 00:02:51.029 based imaging methods that we use,

NOTE Confidence: 0.85592675

00:02:51.030 --> 00:02:52.510 and finally towards the end,

NOTE Confidence: 0.85592675

00:02:52.510 --> 00:02:53.914 I'll tell you what we've been

NOTE Confidence: 0.85592675

00:02:53.914 --> 00:02:56.080 working on in in the vein of neuro

NOTE Confidence: 0.85592675

00:02:56.080 --> 00:02:57.260 psychiatric disorders or models

NOTE Confidence: 0.85592675

00:02:57.260 --> 00:02:59.019 of neuro psychiatric disorders.

NOTE Confidence: 0.8577686

00:03:01.450 --> 00:03:03.618 OK, so first you know this is sort

NOTE Confidence: 0.8577686

00:03:03.618 --> 00:03:05.777 of like a really basic question.

NOTE Confidence: 0.8577686

00:03:05.780 --> 00:03:07.724 I mean, what is a behavioral

NOTE Confidence: 0.8577686

00:03:07.724 --> 00:03:10.100 state or what do we mean by it?

NOTE Confidence: 0.8577686

00:03:10.100 --> 00:03:12.020 And at the end I'm not going to

NOTE Confidence: 0.8577686

00:03:12.020 --> 00:03:14.000 give you any great conceptual answer

NOTE Confidence: 0.8577686

00:03:14.000 --> 00:03:16.160 to that question because I'm not

NOTE Confidence: 0.8577686

00:03:16.220 --> 00:03:18.140 totally sure there there is one,

NOTE Confidence: 0.8577686

00:03:18.140 --> 00:03:20.570 at least in the field and what I will

NOTE Confidence: 0.8577686

00:03:20.570 --> 00:03:23.320 stick to is largely a set of operational

NOTE Confidence: 0.8577686

00:03:23.320 --> 00:03:25.239 definitions and I'll go into that.

NOTE Confidence: 0.8577686

00:03:25.240 --> 00:03:27.720 But in a sort of vague ish way.

NOTE Confidence: 0.8577686

00:03:27.720 --> 00:03:29.904 What we in the field, both both

NOTE Confidence: 0.8577686

00:03:29.904 --> 00:03:31.514 preclinically and clinically often mean.

NOTE Confidence: 0.8577686

00:03:31.520 --> 00:03:33.315 By behavioral state could be

NOTE Confidence: 0.8577686

00:03:33.315 --> 00:03:35.110 levels of arousal or alertness.

NOTE Confidence: 0.8577686

00:03:35.110 --> 00:03:35.758 You know.

NOTE Confidence: 0.8577686

00:03:35.758 --> 00:03:36.082 Obviously,

NOTE Confidence: 0.8577686

00:03:36.082 --> 00:03:38.350 this sort of the mice and this

NOTE Confidence: 0.8577686

00:03:38.418 --> 00:03:40.777 this image here you know sleep wake

NOTE Confidence: 0.8577686

00:03:40.777 --> 00:03:43.091 transitions are a very obvious example

NOTE Confidence: 0.8577686

00:03:43.091 --> 00:03:45.156 of changes in behavioral state,

NOTE Confidence: 0.8577686

00:03:45.160 --> 00:03:47.200 but even just relative attention to

NOTE Confidence: 0.8577686

00:03:47.200 --> 00:03:49.413 what's going on in your environment

NOTE Confidence: 0.8577686

00:03:49.413 --> 00:03:51.759 versus sort of just passively hanging

NOTE Confidence: 0.8577686

00:03:51.759 --> 00:03:54.497 out and being in a very relaxed state.

NOTE Confidence: 0.8577686

00:03:54.500 --> 00:03:55.523 So attention concentration,

NOTE Confidence: 0.8577686

00:03:55.523 --> 00:03:57.228 something that comes up a

NOTE Confidence: 0.8577686

00:03:57.228 --> 00:03:59.158 lot in functional MRI field,

NOTE Confidence: 0.8577686

00:03:59.160 --> 00:04:01.040 sort of resting state versus

NOTE Confidence: 0.8577686

00:04:01.040 --> 00:04:03.200 maybe a task engaged state so.

NOTE Confidence: 0.8577686

00:04:03.200 --> 00:04:06.296 So these are just kind of words that we

NOTE Confidence: 0.8577686

00:04:06.296 --> 00:04:08.670 often used to describe behavioral state

NOTE Confidence: 0.8577686

00:04:08.670 --> 00:04:12.460 at a neural or at a nervous system level.

NOTE Confidence: 0.8577686

00:04:12.460 --> 00:04:15.548 Other words or phrases that often come up,

NOTE Confidence: 0.8577686

00:04:15.550 --> 00:04:16.322 you know,

NOTE Confidence: 0.8577686

00:04:16.322 --> 00:04:17.480 synchrony or correlational

NOTE Confidence: 0.8577686

00:04:17.480 --> 00:04:19.024 structure of brain activity.

NOTE Confidence: 0.8577686

00:04:19.030 --> 00:04:20.595 Default Mode network is something

NOTE Confidence: 0.8577686

00:04:20.595 --> 00:04:23.215 that we hear a lot about specific

NOTE Confidence: 0.8577686

00:04:23.215 --> 00:04:25.191 modulatory systems like acetylcholine

NOTE Confidence: 0.8577686

00:04:25.191 --> 00:04:27.907 or norepinephrine are thought to play

NOTE Confidence: 0.8577686

00:04:27.907 --> 00:04:29.592 important roles in behavioral state

NOTE Confidence: 0.8577686

00:04:29.592 --> 00:04:32.540 and and also sort of notions of top,

NOTE Confidence: 0.8577686

00:04:32.540 --> 00:04:33.530 down or.

NOTE Confidence: 0.8577686

00:04:33.530 --> 00:04:36.995 Higher order regulation of brain function or,

NOTE Confidence: 0.8577686

00:04:37.000 --> 00:04:37.510 say,

NOTE Confidence: 0.8577686

00:04:37.510 --> 00:04:39.550 perceptual ability versus bottom

NOTE Confidence: 0.8577686

00:04:39.550 --> 00:04:42.813 up or or sometimes a sending

NOTE Confidence: 0.8577686

00:04:42.813 --> 00:04:45.277 or sensory driven activity.

NOTE Confidence: 0.8577686

00:04:45.280 --> 00:04:46.489 And of course,

NOTE Confidence: 0.8577686

00:04:46.489 --> 00:04:49.310 all of these things are are profoundly

NOTE Confidence: 0.8577686

00:04:49.392 --> 00:04:52.584 linked to disruption in a number of nurse,

NOTE Confidence: 0.8577686

00:04:52.590 --> 00:04:53.400 psychiatric disorders.

NOTE Confidence: 0.8577686

00:04:53.400 --> 00:04:54.210 Depression, anxiety,

NOTE Confidence: 0.8577686

00:04:54.210 --> 00:04:55.832 attention deficit, you know,

NOTE Confidence: 0.8577686

00:04:55.832 --> 00:04:56.238 schizophrenia,

NOTE Confidence: 0.8577686

00:04:56.238 --> 00:04:58.268 autism so clear mechanistic links

NOTE Confidence: 0.8577686

00:04:58.268 --> 00:05:00.298 between these categories is really

NOTE Confidence: 0.8577686

00:05:00.300 --> 00:05:02.622 still a big topic of investigation

NOTE Confidence: 0.8577686

00:05:02.622 --> 00:05:06.026 in a number of labs and just sort of

NOTE Confidence: 0.8577686

00:05:06.026 --> 00:05:09.229 broadly in the field of neuroscience and.

NOTE Confidence: 0.8577686

00:05:09.230 --> 00:05:10.678 And as I said,

NOTE Confidence: 0.8577686

00:05:10.678 --> 00:05:12.850 I'm not going to provide any

NOTE Confidence: 0.8577686

00:05:12.934 --> 00:05:15.459 any strict links between them.

NOTE Confidence: 0.8577686

00:05:15.460 --> 00:05:16.132 Only to you,

NOTE Confidence: 0.8577686

00:05:16.132 --> 00:05:16.580 you know,

NOTE Confidence: 0.8577686

00:05:16.580 --> 00:05:18.628 sort of provide a sense of how we

NOTE Confidence: 0.8577686

00:05:18.628 --> 00:05:20.461 think about some of these things and

NOTE Confidence: 0.8577686

00:05:20.461 --> 00:05:23.029 and where we are as a field at the moment.

NOTE Confidence: 0.8577686

00:05:23.030 --> 00:05:23.424 OK.

NOTE Confidence: 0.8577686

00:05:23.424 --> 00:05:25.788 So how do we measure behavioral

NOTE Confidence: 0.8577686

00:05:25.788 --> 00:05:26.970 state in rodents?

NOTE Confidence: 0.8577686

00:05:26.970 --> 00:05:29.154 So my lab works entirely in rodents,

NOTE Confidence: 0.8577686

00:05:29.160 --> 00:05:30.009 really in mice,

NOTE Confidence: 0.8577686

00:05:30.009 --> 00:05:32.665 and this is an example of a head fixed

NOTE Confidence: 0.8577686

00:05:32.665 --> 00:05:35.089 mouse of the sort that we might use

NOTE Confidence: 0.8577686

00:05:35.156 --> 00:05:37.328 in any number of our experiments,

NOTE Confidence: 0.8577686

00:05:37.330 --> 00:05:40.147 and in fact many that I'll tell you about.

NOTE Confidence: 0.8577686

00:05:40.150 --> 00:05:42.348 And if you just watch this video,

NOTE Confidence: 0.8577686

00:05:42.350 --> 00:05:43.920 you'll see that the mouse

NOTE Confidence: 0.8577686

00:05:43.920 --> 00:05:45.490 is doing a few things,

NOTE Confidence: 0.8577686

00:05:45.490 --> 00:05:47.380 and I'll point out a couple.

NOTE Confidence: 0.8577686

00:05:47.380 --> 00:05:49.760 So one perhaps most obviously the mouse

NOTE Confidence: 0.8577686

00:05:49.760 --> 00:05:52.289 is running and I think he'll stop for

NOTE Confidence: 0.8577686

00:05:52.289 --> 00:05:54.369 a second and then start up again.

NOTE Confidence: 0.8577686

00:05:54.370 --> 00:05:55.978 But tracking that locomotion

NOTE Confidence: 0.8577686

00:05:55.978 --> 00:05:58.390 at head fixed but locomoting on

NOTE Confidence: 0.8577686

00:05:58.459 --> 00:06:00.427 this freely moving wheel is a

NOTE Confidence: 0.8577686

00:06:00.427 --> 00:06:01.739 very easy marker of

NOTE Confidence: 0.7853542

00:06:01.810 --> 00:06:02.950 something we can.

NOTE Confidence: 0.7853542

00:06:02.950 --> 00:06:05.188 We can sort of distinguish right?

NOTE Confidence: 0.7853542

00:06:05.190 --> 00:06:06.678 Not running, running or

NOTE Confidence: 0.7853542

00:06:06.678 --> 00:06:07.794 questions and locomotion.

NOTE Confidence: 0.7853542

00:06:07.800 --> 00:06:09.678 You can also notice his whiskers

NOTE Confidence: 0.7853542

00:06:09.678 --> 00:06:11.899 and some of his facial musculature

NOTE Confidence: 0.7853542

00:06:11.899 --> 00:06:14.139 is sort of constantly moving.

NOTE Confidence: 0.7853542

00:06:14.140 --> 00:06:16.378 It stops sometimes, then moves again,

NOTE Confidence: 0.7853542

00:06:16.380 --> 00:06:18.240 so these fine motor movements,

NOTE Confidence: 0.7853542

12

00:06:18.240 --> 00:06:19.359 especially in rodents.

NOTE Confidence: 0.7853542

00:06:19.359 --> 00:06:21.597 Whisking is a very obvious one,

NOTE Confidence: 0.7853542

00:06:21.600 --> 00:06:24.498 is another thing we can use to

NOTE Confidence: 0.7853542

00:06:24.498 --> 00:06:25.740 categorise behavioral states.

NOTE Confidence: 0.7853542

00:06:25.740 --> 00:06:26.502 And finally,

NOTE Confidence: 0.7853542

00:06:26.502 --> 00:06:30.638 if you if you sort of zoom in on his eye,

NOTE Confidence: 0.7853542

00:06:30.640 --> 00:06:32.902 here is a little bit subtle

NOTE Confidence: 0.7853542

00:06:32.902 --> 00:06:34.410 in this particular movie.

NOTE Confidence: 0.7853542

00:06:34.410 --> 00:06:36.666 There's not a huge dynamic range,

NOTE Confidence: 0.7853542

00:06:36.670 --> 00:06:37.424 but again,

NOTE Confidence: 0.7853542

00:06:37.424 --> 00:06:38.932 his pupil diameter also

NOTE Confidence: 0.7853542

00:06:38.932 --> 00:06:40.440 fluctuates throughout the movie,

NOTE Confidence: 0.7853542

00:06:40.440 --> 00:06:42.090 and that is another variable

NOTE Confidence: 0.7853542

00:06:42.090 --> 00:06:45.143 that we can use to sort of divide

NOTE Confidence: 0.7853542

00:06:45.143 --> 00:06:46.781 the animals behavioral, state.

NOTE Confidence: 0.7853542

00:06:46.781 --> 00:06:47.684 And so again,

NOTE Confidence: 0.7853542

00:06:47.684 --> 00:06:50.045 I'll be explicit that these are really

NOTE Confidence: 0.7853542

00:06:50.045 --> 00:06:52.505 operational definitions of behavioral state,

NOTE Confidence: 0.7853542

00:06:52.510 --> 00:06:55.149 and there are a number of ideas,

NOTE Confidence: 0.7853542

00:06:55.150 --> 00:06:55.772 some better.

NOTE Confidence: 0.7853542

00:06:55.772 --> 00:06:57.638 Tested and others about neural mechanisms

NOTE Confidence: 0.7853542

00:06:57.638 --> 00:06:59.190 underlying these different variables,

NOTE Confidence: 0.7853542

00:06:59.190 --> 00:07:00.822 but for the moment will really

NOTE Confidence: 0.7853542

00:07:00.822 --> 00:07:02.987 just stick to them as a sort

NOTE Confidence: 0.7853542

00:07:02.987 --> 00:07:04.343 of operational definitions of

NOTE Confidence: 0.7853542

00:07:04.343 --> 00:07:05.718 behavioral States and there's

NOTE Confidence: 0.7853542

00:07:05.718 --> 00:07:07.524 a long list of different labs,

NOTE Confidence: 0.7853542

00:07:07.530 --> 00:07:08.156 including ours.

NOTE Confidence: 0.7853542

00:07:08.156 --> 00:07:10.034 Also just Gardens Lab here at

NOTE Confidence: 0.7853542

00:07:10.034 --> 00:07:11.857 Yale that have worked on this,

NOTE Confidence: 0.7853542

00:07:11.860 --> 00:07:13.666 and we know that these behavioral

NOTE Confidence: 0.7853542

14

00:07:13.666 --> 00:07:15.554 states have a pretty big impact

NOTE Confidence: 0.7853542

00:07:15.554 --> 00:07:17.109 on behavior even in rodents,

NOTE Confidence: 0.7853542

00:07:17.110 --> 00:07:19.077 and so this is just an example

NOTE Confidence: 0.7853542

00:07:19.077 --> 00:07:20.993 of some data from our lab

NOTE Confidence: 0.7853542

00:07:20.993 --> 00:07:22.668 that we published last year.

NOTE Confidence: 0.7853542

00:07:22.670 --> 00:07:24.220 The details aren't terribly important,

NOTE Confidence: 0.7853542

00:07:24.220 --> 00:07:26.780 but on the X axis here I'm plotting.

NOTE Confidence: 0.7853542

00:07:26.780 --> 00:07:28.500 The intensity of a visual

NOTE Confidence: 0.7853542

00:07:28.500 --> 00:07:30.645 stimulus that the animal is being

NOTE Confidence: 0.7853542

00:07:30.645 --> 00:07:32.049 presented with visual contrast

NOTE Confidence: 0.7853542

00:07:32.049 --> 00:07:34.849 and on the Y axis is the animals.

NOTE Confidence: 0.7853542

00:07:34.850 --> 00:07:36.465 Correct performance on this visually

NOTE Confidence: 0.7853542

00:07:36.465 --> 00:07:38.506 guided task and what you'll see

NOTE Confidence: 0.7853542

00:07:38.506 --> 00:07:40.371 is a very characteristic sigmoid

NOTE Confidence: 0.7853542

00:07:40.371 --> 00:07:41.863 relationship between those variables.

NOTE Confidence: 0.7853542

00:07:41.870 --> 00:07:44.327 So as the visual contrast goes up,

NOTE Confidence: 0.7853542

00:07:44.330 --> 00:07:46.090 the animals performance gets better.

NOTE Confidence: 0.7853542

00:07:46.090 --> 00:07:48.166 And if we divide the animals

NOTE Confidence: 0.7853542

00:07:48.166 --> 00:07:49.950 behavior into times when it's,

NOTE Confidence: 0.7853542

00:07:49.950 --> 00:07:51.705 say running versus not running

NOTE Confidence: 0.7853542

00:07:51.705 --> 00:07:53.460 or in the bottom plot,

NOTE Confidence: 0.7853542

00:07:53.460 --> 00:07:56.180 you know when the pupil is large in

NOTE Confidence: 0.7853542

00:07:56.180 --> 00:07:58.129 diameter versus small in diameter.

NOTE Confidence: 0.7853542

00:07:58.130 --> 00:08:00.846 You'll see that those higher arousal states,

NOTE Confidence: 0.7853542

00:08:00.850 --> 00:08:02.800 either from locomotion or pupil,

NOTE Confidence: 0.7853542

00:08:02.800 --> 00:08:04.966 correspond with a left shift in

NOTE Confidence: 0.7853542

00:08:04.966 --> 00:08:07.327 that perceptual curve and also an

NOTE Confidence: 0.7853542

00:08:07.327 --> 00:08:09.019 increase in overall performance.

NOTE Confidence: 0.7853542

00:08:09.020 --> 00:08:09.798 So again,

NOTE Confidence: 0.7853542

00:08:09.798 --> 00:08:11.743 the mechanisms of this are

NOTE Confidence: 0.7853542

00:08:11.743 --> 00:08:12.910 not fully understood,

NOTE Confidence: 0.7853542

00:08:12.910 --> 00:08:15.829 but simply to point out that changes

NOTE Confidence: 0.7853542

00:08:15.829 --> 00:08:17.630 in behavioral state directly

NOTE Confidence: 0.7853542

00:08:17.630 --> 00:08:20.486 correspond to changes in at least

NOTE Confidence: 0.7853542

00:08:20.486 --> 00:08:22.590 perceptual ability in rodents.

NOTE Confidence: 0.7853542

00:08:22.590 --> 00:08:23.582 And so we get.

NOTE Confidence: 0.7853542

00:08:23.582 --> 00:08:25.466 Please jump in with any with any

NOTE Confidence: 0.7853542

00:08:25.466 --> 00:08:27.146 questions if anything comes up.

NOTE Confidence: 0.7853542

00:08:27.150 --> 00:08:27.458 OK,

NOTE Confidence: 0.7853542

00:08:27.458 --> 00:08:29.306 so how do we measure neural

NOTE Confidence: 0.7853542

00:08:29.306 --> 00:08:30.560 activity in our lab?

NOTE Confidence: 0.7853542

00:08:30.560 --> 00:08:33.116 So this is really going to be the meat

NOTE Confidence: 0.7853542

00:08:33.116 --> 00:08:35.824 of the meat of my lab does primarily,

NOTE Confidence: 0.7853542

00:08:35.830 --> 00:08:37.654 but also of the talk and so this

NOTE Confidence: 0.7853542

00:08:37.654 --> 00:08:39.430 is all going to be fluorescence

NOTE Confidence: 0.7853542

00:08:39.430 --> 00:08:41.761 imaging and we're going to in these

NOTE Confidence: 0.7853542

00:08:41.761 --> 00:08:43.257 studies use genetically encoded

NOTE Confidence: 0.7853542

00:08:43.257 --> 00:08:45.428 indicators and I'll talk a bit

NOTE Confidence: 0.7853542

00:08:45.428 --> 00:08:47.514 more about how we get those into

NOTE Confidence: 0.7853542

00:08:47.514 --> 00:08:49.776 the into the brain or into cells,

NOTE Confidence: 0.7853542

00:08:49.780 --> 00:08:51.020 but they can either,

NOTE Confidence: 0.7853542

00:08:51.020 --> 00:08:51.640 you know,

NOTE Confidence: 0.7853542

00:08:51.640 --> 00:08:53.320 be transgenic mice where the mice

NOTE Confidence: 0.7853542

00:08:53.320 --> 00:08:55.360 express the number of these indicators,

NOTE Confidence: 0.7853542

00:08:55.360 --> 00:08:56.910 sort of in their genome,

NOTE Confidence: 0.8324592

00:08:56.910 --> 00:08:59.128 or else we can use, for example,

NOTE Confidence: 0.8324592

00:08:59.128 --> 00:09:00.798 viral vectors to drive expression.

NOTE Confidence: 0.8324592

00:09:00.800 --> 00:09:03.264 I'll come to that just a minute,

NOTE Confidence: 0.8324592

00:09:03.270 --> 00:09:04.682 but probably the most

NOTE Confidence: 0.8324592

00:09:04.682 --> 00:09:06.447 common indicator in our lab,

NOTE Confidence: 0.8324592

00:09:06.450 --> 00:09:08.215 and honestly in the preclinical

NOTE Confidence: 0.8324592

00:09:08.215 --> 00:09:09.980 field of neuroscience in general,

NOTE Confidence: 0.8324592

00:09:09.980 --> 00:09:11.372 are indicators that report

00:09:11.372 --> 00:09:12.764 calcium free concentrations of

00:09:12.764 --> 00:09:14.209 cytosolic calcium within neurons.

00:09:14.210 --> 00:09:16.611 And G camp is probably the most

00:09:16.611 --> 00:09:18.450 ubiquitous and most well known.

00:09:18.450 --> 00:09:20.778 This is a green flora for it's it's

00:09:20.778 --> 00:09:23.079 molecularly a molecule of GFP green

00:09:23.079 --> 00:09:25.154 fluorescent protein fused account module,

00:09:25.160 --> 00:09:27.666 in which calcium binding protein and you

00:09:27.666 --> 00:09:30.810 can sort of see the structure of it here,

00:09:30.810 --> 00:09:33.048 and so you've got this this.

00:09:33.050 --> 00:09:34.538 GFP molecule circularly permuted

00:09:34.538 --> 00:09:37.140 variant of GFP bound to calmodulin and

00:09:37.140 --> 00:09:38.994 so when calcium binds this protein,

00:09:39.000 --> 00:09:40.400 changes its confirmation and

00:09:40.400 --> 00:09:41.800 changes the fluorescent properties.

NOTE Confidence: 0.8324592

00:09:41.800 --> 00:09:43.954 The molecule there are also red

NOTE Confidence: 0.8324592

00:09:43.954 --> 00:09:45.650 shifted variants of these Jr.

NOTE Confidence: 0.8324592

00:09:45.650 --> 00:09:48.002 Camp and Jay are gecko or two variants

NOTE Confidence: 0.8324592

00:09:48.002 --> 00:09:50.547 just that use two different fluorophores,

NOTE Confidence: 0.8324592

00:09:50.550 --> 00:09:52.300 an Ruby and an Apple.

NOTE Confidence: 0.8324592

00:09:52.300 --> 00:09:54.050 These are red shifted floors,

NOTE Confidence: 0.8324592

00:09:54.050 --> 00:09:56.150 but again bound it to calmodulin.

NOTE Confidence: 0.8324592

00:09:56.150 --> 00:09:58.280 Most of these have been developed

NOTE Confidence: 0.8324592

00:09:58.280 --> 00:10:00.110 by the groups that that.

NOTE Confidence: 0.8324592

00:10:00.110 --> 00:10:03.026 Nelia research campus outside of Washington,

NOTE Confidence: 0.8324592

00:10:03.030 --> 00:10:03.395 DC.

NOTE Confidence: 0.8324592

00:10:03.395 --> 00:10:05.220 The other molecule that's going

NOTE Confidence: 0.8324592

00:10:05.220 --> 00:10:07.878 to be important for the talk today

NOTE Confidence: 0.8324592

00:10:07.878 --> 00:10:09.748 is a sensor for acetylcholine.

NOTE Confidence: 0.8324592

00:10:09.750 --> 00:10:10.710 This something actually,

NOTE Confidence: 0.8324592

00:10:10.710 --> 00:10:12.698 the Marine's lab, is used as well.

NOTE Confidence: 0.8324592

00:10:12.698 --> 00:10:15.431 This is a tool that was developed by you

NOTE Confidence: 0.8324592

00:10:15.431 --> 00:10:18.042 Longleys lab at the University of Peking.

NOTE Confidence: 0.8324592

00:10:18.050 --> 00:10:19.958 They called it a Ch 3.0.

NOTE Confidence: 0.8324592

00:10:19.960 --> 00:10:22.186 This is their recent variant of it.

NOTE Confidence: 0.8324592

00:10:22.190 --> 00:10:24.750 It's it's maybe not the most distinct name,

NOTE Confidence: 0.8324592

00:10:24.750 --> 00:10:26.664 but that's what we're going to

NOTE Confidence: 0.8324592

00:10:26.664 --> 00:10:28.876 call it for today, and this is GFP,

NOTE Confidence: 0.8324592

00:10:28.876 --> 00:10:30.859 bound to a variant of a cholinergic

NOTE Confidence: 0.8324592

00:10:30.859 --> 00:10:32.398 muscarinic M2 receptor.

NOTE Confidence: 0.8324592

00:10:32.400 --> 00:10:34.000 But the same idea applies.

NOTE Confidence: 0.8324592

00:10:34.000 --> 00:10:35.660 Basically it's a it's a.

NOTE Confidence: 0.8324592

00:10:35.660 --> 00:10:37.310 Floor for bounded molecule and

NOTE Confidence: 0.8324592

00:10:37.310 --> 00:10:38.960 so when acetylcholine binds it

NOTE Confidence: 0.8324592

00:10:39.017 --> 00:10:41.212 undergoes a conformational shift that

NOTE Confidence: 0.8324592

00:10:41.212 --> 00:10:42.968 changes its fluorescent properties.

NOTE Confidence: 0.8324592

00:10:42.970 --> 00:10:44.590 So why is this useful?

NOTE Confidence: 0.8324592

00:10:44.590 --> 00:10:47.030 So here I'm showing you kind of a

NOTE Confidence: 0.8324592

00:10:47.030 --> 00:10:48.782 cartoon example for calcium, right?

NOTE Confidence: 0.8324592

00:10:48.782 --> 00:10:50.714 So here we've got a neuron.

NOTE Confidence: 0.8324592

00:10:50.720 --> 00:10:52.658 This blue ball expressing G camp.

NOTE Confidence: 0.8324592

00:10:52.660 --> 00:10:54.345 This is fluorescent Reporter and

NOTE Confidence: 0.8324592

00:10:54.345 --> 00:10:56.691 when we shine blue light in this

NOTE Confidence: 0.8324592

00:10:56.691 --> 00:10:58.467 case 480 animator light on this,

NOTE Confidence: 0.8324592

00:10:58.470 --> 00:10:59.439 normally nothing happens.

NOTE Confidence: 0.8324592

00:10:59.439 --> 00:11:01.377 You don't get any green fluorescence,

NOTE Confidence: 0.8324592

00:11:01.380 --> 00:11:02.676 it just sits there.

NOTE Confidence: 0.8324592

00:11:02.676 --> 00:11:04.610 However, when the cell is active,

NOTE Confidence: 0.8324592

00:11:04.610 --> 00:11:06.230 when it fires action potentials,

NOTE Confidence: 0.8324592

00:11:06.230 --> 00:11:08.156 for example, that depolarizes the membrane,

NOTE Confidence: 0.8324592

00:11:08.160 --> 00:11:10.212 it opens voltage gated calcium channels

NOTE Confidence: 0.8324592

22

00:11:10.212 --> 00:11:12.688 which allow calcium to rush into the cell.

NOTE Confidence: 0.8324592

00:11:12.690 --> 00:11:14.046 The calcium then binds.

NOTE Confidence: 0.8324592

00:11:14.046 --> 00:11:17.468 Thejy camp and now in its calcium bound form.

NOTE Confidence: 0.8324592

00:11:17.470 --> 00:11:20.074 When we shine blue light on that,

NOTE Confidence: 0.8324592

00:11:20.080 --> 00:11:22.684 this molecule will now emit green light,

NOTE Confidence: 0.8324592

00:11:22.690 --> 00:11:24.951 and so we can collect these green

NOTE Confidence: 0.8324592

00:11:24.951 --> 00:11:27.170 photons in various imaging modalities.

NOTE Confidence: 0.8324592

00:11:27.170 --> 00:11:28.654 But essentially this increase

NOTE Confidence: 0.8324592

00:11:28.654 --> 00:11:30.880 in green light means that there

NOTE Confidence: 0.8324592

00:11:30.948 --> 00:11:32.653 was an increase in intracellular

NOTE Confidence: 0.8324592

00:11:32.653 --> 00:11:35.234 calcium which we use as a proxy

NOTE Confidence: 0.8324592

00:11:35.234 --> 00:11:36.858 for increased neuronal activity,

NOTE Confidence: 0.8324592

00:11:36.860 --> 00:11:39.044 and so that will be really

NOTE Confidence: 0.8324592

00:11:39.044 --> 00:11:41.339 important for most of this talk.

NOTE Confidence: 0.8324592

00:11:41.340 --> 00:11:43.578 Similarly, this cholinergic Reporter AC H.

NOTE Confidence: 0.8324592

00:11:43.580 --> 00:11:43.950 3.0.

NOTE Confidence: 0.8324592

00:11:43.950 --> 00:11:45.430 So in this case,

NOTE Confidence: 0.8324592

00:11:45.430 --> 00:11:47.386 this is a membrane bound protein,

NOTE Confidence: 0.8324592

00:11:47.390 --> 00:11:49.100 and so when acetylcholine is

NOTE Confidence: 0.8324592

00:11:49.100 --> 00:11:50.810 released from wherever it happens

NOTE Confidence: 0.8651997

00:11:50.866 --> 00:11:53.246 to be released from, if it binds this

NOTE Confidence: 0.8651997

00:11:53.246 --> 00:11:55.570 protein in the membrane of the cell.

NOTE Confidence: 0.8651997

00:11:55.570 --> 00:11:58.098 The same idea. Now suddenly you can get

NOTE Confidence: 0.8651997

00:11:58.098 --> 00:11:59.820 green fluorescence from this molecule,

NOTE Confidence: 0.8651997

00:11:59.820 --> 00:12:01.633 and so in this case the green

NOTE Confidence: 0.8651997

00:12:01.633 --> 00:12:02.947 fluorescence reports the extracellular

NOTE Confidence: 0.8651997

00:12:02.947 --> 00:12:04.390 presence of acetylcholine,

NOTE Confidence: 0.8651997

00:12:04.390 --> 00:12:07.750 which is bound to these membrane receptors.

NOTE Confidence: 0.8651997

00:12:07.750 --> 00:12:11.470 Alright. So the modality that I'm

NOTE Confidence: 0.8651997

00:12:11.470 --> 00:12:14.632 going to talk about most today for

NOTE Confidence: 0.8651997

00:12:14.632 --> 00:12:17.488 imaging is a one photon widefield.

NOTE Confidence: 0.8651997

00:12:17.490 --> 00:12:20.815 We usually call it mesoscopic imaging and

NOTE Confidence: 0.8651997

00:12:20.815 --> 00:12:24.973 what this is is a method for imaging the

NOTE Confidence: 0.8651997

00:12:24.973 --> 00:12:28.090 entire at least dorsal surface of the

NOTE Confidence: 0.8651997

00:12:28.090 --> 00:12:31.501 mouse cortex at one time has some advantages.

NOTE Confidence: 0.8651997

00:12:31.501 --> 00:12:35.109 We can do this through the intact skull,

NOTE Confidence: 0.8651997

00:12:35.110 --> 00:12:37.578 so the surgical invasiveness

NOTE Confidence: 0.8651997

00:12:37.578 --> 00:12:39.429 is relatively low.

NOTE Confidence: 0.8651997

00:12:39.430 --> 00:12:41.524 The the fluorescent reporters that we

NOTE Confidence: 0.8651997

00:12:41.524 --> 00:12:44.518 use are quite right and so you can get

NOTE Confidence: 0.8651997

00:12:44.518 --> 00:12:46.729 really nice signal even through the skull.

NOTE Confidence: 0.8651997

00:12:46.730 --> 00:12:48.728 You can see the entire cortex.

NOTE Confidence: 0.8651997

00:12:48.730 --> 00:12:51.047 As I said, sort of one time.

NOTE Confidence: 0.8651997

00:12:51.050 --> 00:12:52.710 So if you're interested in

NOTE Confidence: 0.8651997

00:12:52.710 --> 00:12:54.038 interactions of different regions,

NOTE Confidence: 0.8651997

00:12:54.040 --> 00:12:55.036 that's fairly straightforward.

NOTE Confidence: 0.8651997

00:12:55.036 --> 00:12:57.360 The perhaps disadvantage is that you cannot

NOTE Confidence: 0.8651997

00:12:57.405 --> 00:12:59.020 resolve individual neurons this way.

NOTE Confidence: 0.8651997

00:12:59.020 --> 00:13:00.680 These are from aerial signals,

NOTE Confidence: 0.8651997

00:13:00.680 --> 00:13:02.340 probably smeared out over at

NOTE Confidence: 0.8651997

00:13:02.340 --> 00:13:04.000 least 100 microns or more.

NOTE Confidence: 0.8651997

00:13:04.000 --> 00:13:06.289 So in some sense it's a little

NOTE Confidence: 0.8651997

00:13:06.289 --> 00:13:07.980 bit akin to do fMRI,

NOTE Confidence: 0.8651997

00:13:07.980 --> 00:13:10.086 or maybe even like a continuous.

NOTE Confidence: 0.8651997

00:13:10.090 --> 00:13:11.482 Local field potential or

NOTE Confidence: 0.8651997

00:13:11.482 --> 00:13:13.222 or EG kind of signal,

NOTE Confidence: 0.8651997

00:13:13.230 --> 00:13:15.980 but still with fairly high

NOTE Confidence: 0.8651997

00:13:15.980 --> 00:13:18.180 spatial and temporal resolution.

NOTE Confidence: 0.8651997

00:13:18.180 --> 00:13:20.028 So this is just one quick example.

NOTE Confidence: 0.8651997

00:13:20.030 --> 00:13:21.608 I want to get everybody oriented

NOTE Confidence: 0.8651997

00:13:21.608 --> 00:13:22.397 a little bit.

NOTE Confidence: 0.8651997

00:13:22.400 --> 00:13:24.464 So this is kind of a cartoon of

NOTE Confidence: 0.8651997

00:13:24.464 --> 00:13:26.099 a microscope that we would use.

NOTE Confidence: 0.8651997

00:13:26.100 --> 00:13:27.714 So we've got big objective that

NOTE Confidence: 0.8651997

00:13:27.714 --> 00:13:29.269 goes over the mouse is head.

NOTE Confidence: 0.8651997

00:13:29.270 --> 00:13:31.910 All of these mice are going to be head fixed,

NOTE Confidence: 0.8651997

00:13:31.910 --> 00:13:33.625 but awaken free to run and so

NOTE Confidence: 0.8651997

00:13:33.625 --> 00:13:35.080 forth is in that movie.

NOTE Confidence: 0.8651997

00:13:35.080 --> 00:13:36.979 I showed you a moment ago and this is

NOTE Confidence: 0.8651997

00:13:36.979 --> 00:13:39.099 a view sort of an unprocessed image of

NOTE Confidence: 0.8651997

00:13:39.099 --> 00:13:41.409 what you can see through the microscope.

NOTE Confidence: 0.8651997

00:13:41.410 --> 00:13:43.786 So this is the front end of the mouse.

NOTE Confidence: 0.8651997

00:13:43.790 --> 00:13:45.722 The mouse is head is pointing

NOTE Confidence: 0.8651997

00:13:45.722 --> 00:13:47.660 up so side side midline.

NOTE Confidence: 0.8651997

00:13:47.660 --> 00:13:49.627 Back end and to all these dark

NOTE Confidence: 0.8651997

00:13:49.627 --> 00:13:51.784 lines that you can see that's the

NOTE Confidence: 0.8651997

00:13:51.784 --> 00:13:53.656 vasculature of the brain of the

NOTE Confidence: 0.8651997

00:13:53.724 --> 00:13:55.848 cortex that shows up quite nicely.

27

NOTE Confidence: 0.8651997

00:13:55.850 --> 00:13:57.740 This is a mouse which is

NOTE Confidence: 0.8651997

00:13:57.740 --> 00:13:59.000 transgenically expressing G cap.

NOTE Confidence: 0.8651997

00:13:59.000 --> 00:14:01.058 So in this case every excitatory

NOTE Confidence: 0.8651997

00:14:01.058 --> 00:14:03.089 neuron in this mouse cortex is

NOTE Confidence: 0.8651997

00:14:03.089 --> 00:14:05.168 expressing G count an when we take

NOTE Confidence: 0.8651997

00:14:05.168 --> 00:14:07.574 a movie we process it a little bit

NOTE Confidence: 0.8651997

00:14:07.574 --> 00:14:09.686 just to look at changes in signals.

NOTE Confidence: 0.8651997

00:14:09.686 --> 00:14:12.209 This is what you get and this is

NOTE Confidence: 0.8651997

00:14:12.209 --> 00:14:14.323 set up three times a little bit

NOTE Confidence: 0.8651997

00:14:14.323 --> 00:14:16.007 faster than than real time,

NOTE Confidence: 0.8651997

00:14:16.010 --> 00:14:18.170 but hopefully you can see this.

NOTE Confidence: 0.8651997

00:14:18.170 --> 00:14:19.805 Pretty interesting and dynamic set

NOTE Confidence: 0.8651997

00:14:19.805 --> 00:14:21.440 of fluctuations that are happening

NOTE Confidence: 0.8651997

00:14:21.493 --> 00:14:22.677 across the entire cortex,

NOTE Confidence: 0.8651997

00:14:22.680 --> 00:14:25.256 and this is for a mouse that's just

NOTE Confidence: 0.8651997

00:14:25.256 --> 00:14:26.722 sitting there, not doing anything,

NOTE Confidence: 0.8651997

00:14:26.722 --> 00:14:29.047 so this is sort of a very quick

NOTE Confidence: 0.8651997

00:14:29.047 --> 00:14:30.782 introduction to how dynamic the

NOTE Confidence: 0.8651997

00:14:30.782 --> 00:14:33.233 cortex is even when we are supposedly

NOTE Confidence: 0.8651997

00:14:33.233 --> 00:14:34.903 not doing anything at all,

NOTE Confidence: 0.8651997

00:14:34.910 --> 00:14:36.250 just just sitting there.

NOTE Confidence: 0.8651997

00:14:36.250 --> 00:14:38.260 And so this work was described

NOTE Confidence: 0.8651997

00:14:38.325 --> 00:14:40.411 in a couple of papers that we

NOTE Confidence: 0.8651997

00:14:40.411 --> 00:14:41.305 published just last

NOTE Confidence: 0.87164307

00:14:41.375 --> 00:14:43.606 year. If you're interested in more details,

NOTE Confidence: 0.87164307

00:14:43.610 --> 00:14:45.598 but I'm going to use this method

NOTE Confidence: 0.87164307

00:14:45.598 --> 00:14:47.469 for the next several slides,

NOTE Confidence: 0.87164307

00:14:47.470 --> 00:14:49.160 so just as a reminder.

NOTE Confidence: 0.87164307

00:14:49.160 --> 00:14:51.896 This is the top down view of the mouse.

NOTE Confidence: 0.87164307

00:14:51.900 --> 00:14:53.116 Brain Front is up.

NOTE Confidence: 0.87164307

00:14:53.116 --> 00:14:54.940 Back is down side to side.

NOTE Confidence: 0.8342438

00:14:57.290 --> 00:14:59.537 So while that last mouse was transgenic,

NOTE Confidence: 0.8342438

00:14:59.540 --> 00:15:01.556 much of the data that I'm going to

NOTE Confidence: 0.8342438

00:15:01.556 --> 00:15:03.485 show you today uses also another

NOTE Confidence: 0.8342438

00:15:03.485 --> 00:15:05.525 new method that we've developed in

NOTE Confidence: 0.8342438

00:15:05.592 --> 00:15:07.587 collaboration with Mike Rares Lab.

NOTE Confidence: 0.8342438

00:15:07.590 --> 00:15:08.654 Also here at Yale.

NOTE Confidence: 0.8342438

00:15:08.654 --> 00:15:11.131 And this is to use viral vectors to

NOTE Confidence: 0.8342438

00:15:11.131 --> 00:15:13.171 drive the expression of transgenic

NOTE Confidence: 0.8342438

00:15:13.171 --> 00:15:15.575 proteins rather than having to make a

NOTE Confidence: 0.8342438

00:15:15.575 --> 00:15:17.894 mouse where you say knock in a gene.

NOTE Confidence: 0.8342438

00:15:17.894 --> 00:15:19.826 This is, it's not terribly complex,

NOTE Confidence: 0.8342438

00:15:19.830 --> 00:15:22.728 but it's it takes a lot of work and,

NOTE Confidence: 0.8342438

00:15:22.730 --> 00:15:25.050 and so this is in some respects a

NOTE Confidence: 0.8342438

00:15:25.050 --> 00:15:27.213 much easier way to get transgenic

NOTE Confidence: 0.8342438

00:15:27.213 --> 00:15:28.347 expression in mice.

NOTE Confidence: 0.8342438

00:15:28.350 --> 00:15:31.650 And so in this case we take a mouse pup.

NOTE Confidence: 0.8342438

00:15:31.650 --> 00:15:33.474 This really only works well in

NOTE Confidence: 0.8342438

00:15:33.474 --> 00:15:35.609 the first couple of neonatal days,

NOTE Confidence: 0.8342438

00:15:35.610 --> 00:15:37.590 and we take a viral vector

NOTE Confidence: 0.8342438

00:15:37.590 --> 00:15:38.580 adeno associated virus.

NOTE Confidence: 0.8342438

00:15:38.580 --> 00:15:39.570 In this case,

NOTE Confidence: 0.8342438

00:15:39.570 --> 00:15:40.890 this is pretty ubiquitous

NOTE Confidence: 0.8342438

00:15:40.890 --> 00:15:42.210 in neuroscience these days,

NOTE Confidence: 0.8342438

00:15:42.210 --> 00:15:44.240 and it turns out that the serotype

NOTE Confidence: 0.8342438

00:15:44.240 --> 00:15:46.293 9 variant of AAV crosses the

NOTE Confidence: 0.8342438

00:15:46.293 --> 00:15:48.148 blood brain barrier really well,

NOTE Confidence: 0.8342438

00:15:48.150 --> 00:15:50.460 especially in the early post Natal period.

NOTE Confidence: 0.8342438

00:15:50.460 --> 00:15:53.100 So we take a virus in this case.

NOTE Confidence: 0.8342438

00:15:53.100 --> 00:15:54.090 Two different viruses,

NOTE Confidence: 0.8342438

00:15:54.090 --> 00:15:55.410 one driving our camp,

NOTE Confidence: 0.8342438

00:15:55.410 --> 00:15:57.115 which is this redshifted calcium

NOTE Confidence: 0.8342438

00:15:57.115 --> 00:15:58.479 indicator that I mentioned?

NOTE Confidence: 0.8342438

00:15:58.480 --> 00:16:01.427 And one driving this H 3.0 cholinergic

NOTE Confidence: 0.8342438

00:16:01.427 --> 00:16:04.107 signal so we mix those viruses

NOTE Confidence: 0.8342438

00:16:04.107 --> 00:16:07.222 together and we inject them into the

NOTE Confidence: 0.8342438

00:16:07.313 --> 00:16:09.785 transverse sinus is of this mouse

NOTE Confidence: 0.8342438

00:16:09.785 --> 00:16:12.572 is brain into P0 to P1 period and

NOTE Confidence: 0.8342438

00:16:12.572 --> 00:16:15.234 what you see here on the right is

NOTE Confidence: 0.8342438

00:16:15.234 --> 00:16:17.006 some Histology demonstrating the

NOTE Confidence: 0.8342438

00:16:17.006 --> 00:16:19.416 massive and robust and widespread

NOTE Confidence: 0.8342438

00:16:19.416 --> 00:16:22.261 expression of both the green

NOTE Confidence: 0.8342438

00:16:22.261 --> 00:16:23.968 fluorescing cholinergic indicator,

NOTE Confidence: 0.8342438

00:16:23.970 --> 00:16:26.130 the red fluorescent calcium indicator,

NOTE Confidence: 0.8342438

00:16:26.130 --> 00:16:29.028 pretty much throughout the entire brain.

NOTE Confidence: 0.8342438

00:16:29.030 --> 00:16:30.660 So this neonatal virus injection

NOTE Confidence: 0.8342438

00:16:30.660 --> 00:16:32.290 protocol is really incredibly powerful.

NOTE Confidence: 0.8342438

00:16:32.290 --> 00:16:34.240 Works for anything that you can

NOTE Confidence: 0.8342438

00:16:34.240 --> 00:16:35.215 express via AV,

NOTE Confidence: 0.8342438

00:16:35.220 --> 00:16:38.060 and in fact I'll show you some some

NOTE Confidence: 0.8342438

00:16:38.060 --> 00:16:40.435 additional data at the end of the talk.

NOTE Confidence: 0.8342438

00:16:40.440 --> 00:16:42.396 For some more nervous psychiatric models,

NOTE Confidence: 0.8342438

00:16:42.400 --> 00:16:44.250 but regardless that this isn't

NOTE Confidence: 0.8342438

00:16:44.250 --> 00:16:46.432 otherwise wild type mouse that you

NOTE Confidence: 0.8342438

00:16:46.432 --> 00:16:48.584 just sort of picked out of the cage.

NOTE Confidence: 0.8342438

00:16:48.590 --> 00:16:51.446 And now you can get really nice

NOTE Confidence: 0.8342438

00:16:51.446 --> 00:16:53.640 expression of these indicators.

NOTE Confidence: 0.8342438

00:16:53.640 --> 00:16:54.456 And so again,

NOTE Confidence: 0.8342438

00:16:54.456 --> 00:16:56.088 this was first described in a

NOTE Confidence: 0.8342438

00:16:56.088 --> 00:16:57.529 paper published last year.

NOTE Confidence: 0.8342438

00:16:57.530 --> 00:16:59.110 An much more methodological description

NOTE Confidence: 0.8342438

00:16:59.110 --> 00:17:01.571 of this is in this paper by Hamodia

NOTE Confidence: 0.8342438

00:17:01.571 --> 00:17:03.209 doll from last year as well,

NOTE Confidence: 0.8342438

00:17:03.210 --> 00:17:05.359 and it was only hamodia made by

NOTE Confidence: 0.8342438

00:17:05.359 --> 00:17:07.500 Chris Lab that they really sort

NOTE Confidence: 0.8342438

00:17:07.500 --> 00:17:09.028 of pioneered this tool.

NOTE Confidence: 0.8342438

00:17:09.030 --> 00:17:11.179 Alright, so we're going to use now.

NOTE Confidence: 0.8342438

00:17:11.180 --> 00:17:12.645 This dual expression approach of

NOTE Confidence: 0.8342438

00:17:12.645 --> 00:17:14.110 the red shifted calcium indicator

NOTE Confidence: 0.8342438

00:17:14.162 --> 00:17:15.742 in the green fluorescent cholinergic

NOTE Confidence: 0.8342438

00:17:15.742 --> 00:17:17.006 indicator for some studies.

NOTE Confidence: 0.8342438

00:17:17.010 --> 00:17:18.846 I'm going to show you about.

NOTE Confidence: 0.8342438

00:17:18.850 --> 00:17:19.172 Alright,

NOTE Confidence: 0.8342438

00:17:19.172 --> 00:17:21.426 this is probably going to be the

NOTE Confidence: 0.8342438

00:17:21.426 --> 00:17:23.238 busiest slide that I show you

NOTE Confidence: 0.8342438

00:17:23.238 --> 00:17:24.066 through the talk,

NOTE Confidence: 0.8342438

00:17:24.070 --> 00:17:26.065 so I'm going to walk you through

NOTE Confidence: 0.8342438

00:17:26.065 --> 00:17:27.450 it in some stages,

NOTE Confidence: 0.8342438

00:17:27.450 --> 00:17:29.298 but there's there are a few

NOTE Confidence: 0.8342438

00:17:29.298 --> 00:17:30.830 important things to point out,

NOTE Confidence: 0.8342438

00:17:30.830 --> 00:17:32.979 so this is work that was done

NOTE Confidence: 0.8342438

00:17:32.979 --> 00:17:33.900 by sweater Lohani,

NOTE Confidence: 0.8342438

00:17:33.900 --> 00:17:35.776 who is a postdoc in the carbon

NOTE Confidence: 0.8342438

00:17:35.776 --> 00:17:37.580 lab here and Andrew Moberly,

NOTE Confidence: 0.8342438

00:17:37.580 --> 00:17:39.518 whose adjoint postdoc between my lab.

NOTE Confidence: 0.8342438

00:17:39.520 --> 00:17:40.747 Not injustice Liberia.

NOTE Confidence: 0.8342438

00:17:40.747 --> 00:17:43.997 So first this is a similar cartoon to

NOTE Confidence: 0.8342438

00:17:43.997 --> 00:17:46.832 what I just showed you a few minutes ago.

NOTE Confidence: 0.8342438

00:17:46.840 --> 00:17:49.120 Only instead of there being one CMOS camera,

NOTE Confidence: 0.8207578

00:17:49.120 --> 00:17:50.830 we now have two CMOS cameras,

NOTE Confidence: 0.8207578

00:17:50.830 --> 00:17:52.870 one to detect the red signal which is

NOTE Confidence: 0.8207578

00:17:52.870 --> 00:17:55.060 calcium in this case and wanted to take

NOTE Confidence: 0.8207578

00:17:55.060 --> 00:17:57.099 the green signal which is acetylcholine,

NOTE Confidence: 0.8207578

00:17:57.100 --> 00:18:00.322 and in this case, but again you've got the

NOTE Confidence: 0.8207578

00:18:00.322 --> 00:18:03.294 mouse sitting on the wheel and so forth.

NOTE Confidence: 0.8207578

00:18:03.300 --> 00:18:05.724 So these are just a couple images similar

NOTE Confidence: 0.8207578

00:18:05.724 --> 00:18:08.487 to you know the movie I just showed you.

NOTE Confidence: 0.8207578

00:18:08.490 --> 00:18:10.302 Again we're looking down on the

NOTE Confidence: 0.8207578

00:18:10.302 --> 00:18:12.447 top of the mouse brain up, up.

NOTE Confidence: 0.8207578

00:18:12.447 --> 00:18:14.823 Is that the front of the brain down

NOTE Confidence: 0.8207578

00:18:14.823 --> 00:18:17.482 is the back and here we've got signals

NOTE Confidence: 0.8207578

00:18:17.482 --> 00:18:20.466 in the top row for the H 3.0 and in

NOTE Confidence: 0.8207578

00:18:20.466 --> 00:18:22.870 the bottom row our camp and we can

NOTE Confidence: 0.8207578

00:18:22.870 --> 00:18:24.440 divide this these cortical regions

NOTE Confidence: 0.8207578

00:18:24.505 --> 00:18:26.871 into different chunks by a number of

NOTE Confidence: 0.8207578

00:18:26.871 --> 00:18:28.944 different methods and I'll talk a bit

NOTE Confidence: 0.8207578

00:18:28.944 --> 00:18:31.072 more about that in a moment as well.

NOTE Confidence: 0.8207578

00:18:31.072 --> 00:18:33.560 But here you can sort of make out.

NOTE Confidence: 0.8207578

00:18:33.560 --> 00:18:36.566 I've drawn on an ROI or region of interest.

NOTE Confidence: 0.8207578

00:18:36.570 --> 00:18:38.656 It's sort of a little circle ish

NOTE Confidence: 0.8207578

00:18:38.656 --> 00:18:40.570 thing around a frontal region.

NOTE Confidence: 0.8207578

00:18:40.570 --> 00:18:42.922 This sort of motor cortex and also

NOTE Confidence: 0.8207578

00:18:42.922 --> 00:18:44.869 another here around the back region

NOTE Confidence: 0.8207578

00:18:44.869 --> 00:18:46.913 or visual areas and so in those

NOTE Confidence: 0.8207578

00:18:46.980 --> 00:18:49.507 areas we can now plot the fluorescent

NOTE Confidence: 0.8207578

00:18:49.507 --> 00:18:51.538 signal that's coming from those two

NOTE Confidence: 0.8207578

00:18:51.538 --> 00:18:54.555 areas as a function of time so we can

NOTE Confidence: 0.8207578

00:18:54.555 --> 00:18:56.745 see how these signals vary overtime

NOTE Confidence: 0.8207578

00:18:56.745 --> 00:18:59.098 for these two different regions.

NOTE Confidence: 0.8207578

00:18:59.100 --> 00:19:02.100 And so first I just show you the our camp

NOTE Confidence: 0.8207578

00:19:02.177 --> 00:19:05.397 data and so now you can see in purple above.

NOTE Confidence: 0.8207578

00:19:05.400 --> 00:19:07.822 This is the variation in that red

NOTE Confidence: 0.8207578

00:19:07.822 --> 00:19:09.225 fluorescence corresponding to cortical

NOTE Confidence: 0.8207578

00:19:09.225 --> 00:19:11.374 neuron activity via calcium in V1 in

NOTE Confidence: 0.8207578

00:19:11.374 --> 00:19:13.587 purple and then just below that in red.

NOTE Confidence: 0.8207578

00:19:13.590 --> 00:19:15.450 Is this this motor region and

NOTE Confidence: 0.8207578

00:19:15.450 --> 00:19:17.688 below all of that at the bottom?

NOTE Confidence: 0.8207578

00:19:17.690 --> 00:19:19.260 I've also drawn traces that

NOTE Confidence: 0.8207578

00:19:19.260 --> 00:19:20.516 correspond face map here.

NOTE Confidence: 0.8207578

00:19:20.520 --> 00:19:22.100 This is the facial musculature.

NOTE Confidence: 0.8207578

00:19:22.100 --> 00:19:23.201 It's mostly whisking,

NOTE Confidence: 0.8207578

00:19:23.201 --> 00:19:26.190 so this shows you sort of when the

NOTE Confidence: 0.8207578

00:19:26.190 --> 00:19:28.612 animal is whisking and then when it

NOTE Confidence: 0.8207578

00:19:28.612 --> 00:19:30.995 stops and when it was a bit more.

NOTE Confidence: 0.8207578

00:19:31.000 --> 00:19:31.369 Similarly,

NOTE Confidence: 0.8207578

00:19:31.369 --> 00:19:33.583 we have the pupil diameter plotted

NOTE Confidence: 0.8207578

00:19:33.583 --> 00:19:35.780 as a continuous function of time,

NOTE Confidence: 0.8207578

00:19:35.780 --> 00:19:37.988 and then we also have running

NOTE Confidence: 0.8207578

00:19:37.988 --> 00:19:39.460 speed on the wheel.

NOTE Confidence: 0.8207578

00:19:39.460 --> 00:19:42.036 You can see that these variables are

NOTE Confidence: 0.8207578

00:19:42.036 --> 00:19:43.879 roughly correlated with each other,

NOTE Confidence: 0.8207578

00:19:43.880 --> 00:19:45.570 and that's something that we

NOTE Confidence: 0.8207578

00:19:45.570 --> 00:19:47.260 see typically that there's some

NOTE Confidence: 0.8207578

00:19:47.316 --> 00:19:49.396 underlying state variable of arousal,

NOTE Confidence: 0.8207578

00:19:49.400 --> 00:19:51.105 whatever that means that is

NOTE Confidence: 0.8207578

00:19:51.105 --> 00:19:52.810 strongly correlated with a number

NOTE Confidence: 0.8207578

00:19:52.871 --> 00:19:54.547 of these behavioral variables,

NOTE Confidence: 0.8207578

00:19:54.550 --> 00:19:57.224 and so you'll note that the fluorescent

NOTE Confidence: 0.8207578

00:19:57.224 --> 00:19:58.970 signals the purple and red,

NOTE Confidence: 0.8207578

00:19:58.970 --> 00:20:00.332 actually agree roughly.

NOTE Confidence: 0.8207578

00:20:00.332 --> 00:20:02.602 With the fluctuations in these

NOTE Confidence: 0.8207578

00:20:02.602 --> 00:20:04.730 behavioral state variables as well.

NOTE Confidence: 0.8207578

00:20:04.730 --> 00:20:07.054 And so this is the calcium signal.

NOTE Confidence: 0.8207578

00:20:07.060 --> 00:20:09.058 Again, correspond to local cortical activity.

NOTE Confidence: 0.8207578

00:20:09.060 --> 00:20:11.013 We can do the same thing looking

NOTE Confidence: 0.8207578

00:20:11.013 --> 00:20:12.720 at the green fluorescence,

NOTE Confidence: 0.8207578

00:20:12.720 --> 00:20:14.390 which is the acetylcholine readout.

NOTE Confidence: 0.8207578

00:20:14.390 --> 00:20:14.996 And again,

NOTE Confidence: 0.8207578

00:20:14.996 --> 00:20:16.511 you see fluctuations in the

NOTE Confidence: 0.8207578

00:20:16.511 --> 00:20:17.853 acetylcholine that also track

NOTE Confidence: 0.8207578

00:20:17.853 --> 00:20:19.377 these behavioral state variables,

NOTE Confidence: 0.8207578

00:20:19.380 --> 00:20:21.704 and we can get that for both.

NOTE Confidence: 0.8207578

00:20:21.710 --> 00:20:22.658 In this case,

NOTE Confidence: 0.8207578

00:20:22.658 --> 00:20:25.380 this motor region is also the visual cortex,

NOTE Confidence: 0.8207578

00:20:25.380 --> 00:20:28.316 so there's two main points then that I'd

NOTE Confidence: 0.8207578

00:20:28.316 --> 00:20:31.449 like you to take from this whole figure.

NOTE Confidence: 0.8207578

00:20:31.450 --> 00:20:34.110 The first is that as you note,

NOTE Confidence: 0.8207578

00:20:34.110 --> 00:20:36.770 these signals are very dynamic in time,

NOTE Confidence: 0.8207578

00:20:36.770 --> 00:20:39.050 so they they fluctuate at both

NOTE Confidence: 0.8207578

00:20:39.050 --> 00:20:40.570 fast and slow timescales.

NOTE Confidence: 0.840474

00:20:40.570 --> 00:20:42.470 The slower timescales correspond roughly

NOTE Confidence: 0.840474

00:20:42.470 --> 00:20:44.370 to these behavioral state transitions,

NOTE Confidence: 0.840474

00:20:44.370 --> 00:20:46.842 probably locomotion and pupil are the

NOTE Confidence: 0.840474

00:20:46.842 --> 00:20:50.070 easiest to see as they go up and down.

NOTE Confidence: 0.840474

00:20:50.070 --> 00:20:52.751 You see you sort of corresponding variation

NOTE Confidence: 0.840474

00:20:52.751 --> 00:20:55.896 in the in both the cholinergic in that

NOTE Confidence: 0.840474

00:20:55.896 --> 00:20:59.073 in the calcium signal so there's a lot

NOTE Confidence: 0.840474

00:20:59.073 --> 00:21:01.437 of temporal dynamics and the other.

NOTE Confidence: 0.840474

00:21:01.440 --> 00:21:03.090 Point is that there's a lot

NOTE Confidence: 0.840474

00:21:03.090 --> 00:21:03.915 of spatial heterogeneity,

NOTE Confidence: 0.840474

00:21:03.920 --> 00:21:06.349 and that perhaps you can appreciate most

NOTE Confidence: 0.840474

00:21:06.349 --> 00:21:08.982 just looking at the images at the top so

NOTE Confidence: 0.840474

00:21:08.982 --> 00:21:11.738 you can also see that in the traces as well.

NOTE Confidence: 0.840474

00:21:11.740 --> 00:21:14.164 And for calcium, I mean maybe that's not

NOTE Confidence: 0.840474

00:21:14.164 --> 00:21:16.208 surprising in the sense that different areas

NOTE Confidence: 0.840474

00:21:16.208 --> 00:21:18.769 of the brain or or at least the cortex,

NOTE Confidence: 0.840474

00:21:18.770 --> 00:21:19.938 are doing different things

00:21:19.938 --> 00:21:20.814 at different times.

00:21:20.820 --> 00:21:22.962 OK, it was perhaps a little surprising

00:21:22.962 --> 00:21:24.340 for the acetylcholine in that,

00:21:24.340 --> 00:21:26.167 at least in the early days of

00:21:26.167 --> 00:21:27.860 the field and early meaning,

00:21:27.860 --> 00:21:28.820 say, 50 years ago,

00:21:28.820 --> 00:21:30.916 there was a sense that some of these

00:21:30.916 --> 00:21:32.426 brainstem modulators might really be

00:21:32.426 --> 00:21:34.590 just sort of global arousal signals,

00:21:34.590 --> 00:21:36.648 and so you might have expected that.

00:21:36.650 --> 00:21:38.402 OK, you know when arousal goes

00:21:38.402 --> 00:21:39.278 up acetylcholine everywhere,

00:21:39.280 --> 00:21:40.159 it goes up,

00:21:40.159 --> 00:21:41.917 and then when arousal goes downhill,

00:21:41.920 --> 00:21:44.020 going everywhere goes down every sort of.

00:21:44.020 --> 00:21:45.855 A simple readout of behavioral

NOTE Confidence: 0.840474

00:21:45.855 --> 00:21:47.690 state and what we find,

NOTE Confidence: 0.840474

00:21:47.690 --> 00:21:49.525 and this isn't this isn't

NOTE Confidence: 0.840474

00:21:49.525 --> 00:21:50.259 necessarily surprising,

NOTE Confidence: 0.840474

00:21:50.260 --> 00:21:51.692 especially given recent anatomical

NOTE Confidence: 0.840474

00:21:51.692 --> 00:21:53.840 findings about the diversity of cholinergic

NOTE Confidence: 0.840474

00:21:53.886 --> 00:21:55.398 projections throughout the brain.

NOTE Confidence: 0.840474

00:21:55.400 --> 00:21:55.960 But nevertheless,

NOTE Confidence: 0.840474

00:21:55.960 --> 00:21:57.920 what you can see here is that

NOTE Confidence: 0.840474

00:21:57.920 --> 00:21:59.760 even the acetylcholine is

NOTE Confidence: 0.840474

00:21:59.760 --> 00:22:01.266 incredibly spatially heterogeneous.

NOTE Confidence: 0.840474

00:22:01.270 --> 00:22:03.145 And so acetylcholine release in

NOTE Confidence: 0.840474

00:22:03.145 --> 00:22:05.828 different parts of the cortex can be

NOTE Confidence: 0.840474

00:22:05.828 --> 00:22:07.673 remarkably UN coupled from release

NOTE Confidence: 0.840474

00:22:07.673 --> 00:22:09.709 in other locations in the cortex.

NOTE Confidence: 0.840474

00:22:09.710 --> 00:22:10.727 So so, really.

NOTE Confidence: 0.840474

00:22:10.727 --> 00:22:12.422 Acetylcholine is not just sort

NOTE Confidence: 0.840474

00:22:12.422 --> 00:22:14.190 of a generic signal.

NOTE Confidence: 0.840474

00:22:14.190 --> 00:22:19.380 Of overall state, but in fact as a as a,

NOTE Confidence: 0.840474

00:22:19.380 --> 00:22:20.750 you know,

NOTE Confidence: 0.840474

00:22:20.750 --> 00:22:23.490 primary component of dynamic

NOTE Confidence: 0.840474

00:22:23.490 --> 00:22:24.860 cortical variables.

NOTE Confidence: 0.840474

00:22:24.860 --> 00:22:26.690 And just to finally make that

NOTE Confidence: 0.840474

00:22:26.690 --> 00:22:28.690 that last point a little bit,

NOTE Confidence: 0.840474

00:22:28.690 --> 00:22:30.658 these black traces that you see here and

NOTE Confidence: 0.840474

00:22:30.658 --> 00:22:32.414 here are the instantaneous correlations

NOTE Confidence: 0.840474

00:22:32.414 --> 00:22:34.424 between the two cortical regions,

NOTE Confidence: 0.840474

00:22:34.430 --> 00:22:36.974 and so you can just see there that.

NOTE Confidence: 0.840474

00:22:36.980 --> 00:22:37.334 So,

NOTE Confidence: 0.840474

00:22:37.334 --> 00:22:38.042 for example,

NOTE Confidence: 0.840474

00:22:38.042 --> 00:22:39.812 the correlation of acetylcholine release

NOTE Confidence: 0.840474

44

00:22:39.812 --> 00:22:41.768 between M2 and V1 starts out high,

NOTE Confidence: 0.840474

00:22:41.770 --> 00:22:43.996 then it actually drops a little bit,

NOTE Confidence: 0.840474

00:22:44.000 --> 00:22:45.600 then it goes up again.

NOTE Confidence: 0.840474

00:22:45.600 --> 00:22:47.622 So just the correlational structure of

NOTE Confidence: 0.840474

00:22:47.622 --> 00:22:50.059 these signals varies as a function of time,

NOTE Confidence: 0.840474

00:22:50.060 --> 00:22:51.998 so this is really about religious

NOTE Confidence: 0.840474

00:22:51.998 --> 00:22:53.672 descriptive view of the kinds

NOTE Confidence: 0.840474

00:22:53.672 --> 00:22:55.277 of studies that we're doing.

NOTE Confidence: 0.840474

00:22:55.280 --> 00:22:57.380 And so now let me go into a little bit

NOTE Confidence: 0.840474

00:22:57.438 --> 00:22:59.426 more detail of some of our analysis.

NOTE Confidence: 0.8580042

00:23:01.880 --> 00:23:04.088 So the first thing that we do is

NOTE Confidence: 0.8580042

00:23:04.088 --> 00:23:06.855 spend a good amount of time trying

NOTE Confidence: 0.8580042

00:23:06.855 --> 00:23:08.567 to understand what behavioral

NOTE Confidence: 0.8580042

00:23:08.567 --> 00:23:11.837 state means or what some of these

NOTE Confidence: 0.8580042

00:23:11.837 --> 00:23:13.220 transitions mean quantitatively.

NOTE Confidence: 0.8580042

00:23:13.220 --> 00:23:16.739 An for the next little part of the talk.

NOTE Confidence: 0.8580042

00:23:16.740 --> 00:23:19.692 I'm really going to focus on the two

NOTE Confidence: 0.8580042

00:23:19.692 --> 00:23:22.207 major motor signals that we study,

NOTE Confidence: 0.8580042

00:23:22.210 --> 00:23:24.170 locomotion and facial movement here.

NOTE Confidence: 0.8580042

00:23:24.170 --> 00:23:25.778 It's called face map.

NOTE Confidence: 0.8580042

00:23:25.778 --> 00:23:29.132 This is named after the software that we

NOTE Confidence: 0.8580042

00:23:29.132 --> 00:23:32.142 use to extract these these movement signals.

NOTE Confidence: 0.8580042

00:23:32.150 --> 00:23:33.654 Primarily corresponds to whisking

NOTE Confidence: 0.8580042

00:23:33.654 --> 00:23:35.910 in detail if anyone is interested.

NOTE Confidence: 0.8580042

00:23:35.910 --> 00:23:37.530 It's essentially a principle

NOTE Confidence: 0.8580042

00:23:37.530 --> 00:23:39.150 component based decomposition of

NOTE Confidence: 0.8580042

00:23:39.150 --> 00:23:41.167 the video ography of the face,

NOTE Confidence: 0.8580042

00:23:41.170 --> 00:23:44.050 so you basically take a movie of of the

NOTE Confidence: 0.8580042

00:23:44.050 --> 00:23:47.101 animals entire face and you decompose it

NOTE Confidence: 0.8580042

00:23:47.101 --> 00:23:49.639 via principal component analysis to get

NOTE Confidence: 0.8580042

00:23:49.639 --> 00:23:52.075 a bunch of features that describe that.

NOTE Confidence: 0.8580042

00:23:52.080 --> 00:23:53.960 But nevertheless most of it

NOTE Confidence: 0.8580042

00:23:53.960 --> 00:23:55.840 really just agrees with whisking.

NOTE Confidence: 0.8580042

00:23:55.840 --> 00:23:58.090 That's that's the most dominant component.

NOTE Confidence: 0.8580042

00:23:58.090 --> 00:23:59.970 So looking at these traces,

NOTE Confidence: 0.8580042

00:23:59.970 --> 00:24:02.286 you'll know a few things so.

NOTE Confidence: 0.8580042

00:24:02.290 --> 00:24:03.830 Locomotion is perhaps easiest, right?

NOTE Confidence: 0.8580042

00:24:03.830 --> 00:24:05.684 So the animals just sitting there

NOTE Confidence: 0.8580042

00:24:05.684 --> 00:24:07.530 quiet for most of the time,

NOTE Confidence: 0.8580042

00:24:07.530 --> 00:24:09.476 and this sort of pinkish box sort

NOTE Confidence: 0.8580042

00:24:09.476 --> 00:24:11.079 of illustrates this sustained low

NOTE Confidence: 0.8580042

00:24:11.079 --> 00:24:12.150 level of locomotion.

NOTE Confidence: 0.8580042

00:24:12.150 --> 00:24:13.690 Really, no locomotion at all,

NOTE Confidence: 0.8580042

00:24:13.690 --> 00:24:14.918 and then later on,

NOTE Confidence: 0.8580042

00:24:14.918 --> 00:24:16.146 the animal starts running.

NOTE Confidence: 0.8580042

00:24:16.150 --> 00:24:18.494 It has these two little bursts of running

NOTE Confidence: 0.8580042

00:24:18.494 --> 00:24:21.075 and then a slightly longer period as well.

NOTE Confidence: 0.8580042

00:24:21.080 --> 00:24:22.928 And note the time scale here.

NOTE Confidence: 0.8580042

00:24:22.930 --> 00:24:25.079 This is 25 seconds for the bar,

NOTE Confidence: 0.8580042

00:24:25.080 --> 00:24:27.572 so so this this whole trace is

NOTE Confidence: 0.8580042

00:24:27.572 --> 00:24:30.207 actually a fairly long period of time.

NOTE Confidence: 0.8580042

00:24:30.210 --> 00:24:33.200 And then if you look at the at the facial

NOTE Confidence: 0.8580042

00:24:33.281 --> 00:24:35.836 movement in the in the below trace,

NOTE Confidence: 0.8580042

00:24:35.840 --> 00:24:37.820 you see that it fluctuates much,

NOTE Confidence: 0.8580042

00:24:37.820 --> 00:24:38.813 much more rapidly,

NOTE Confidence: 0.8580042

00:24:38.813 --> 00:24:40.137 but there's some agreement,

NOTE Confidence: 0.8580042

00:24:40.140 --> 00:24:42.788 especially if you look over the right side,

NOTE Confidence: 0.8580042

00:24:42.790 --> 00:24:46.366 you get these sort of sustained changes that

NOTE Confidence: 0.8580042

00:24:46.366 --> 00:24:49.577 correspond to to the balance of locomotion.

NOTE Confidence: 0.8580042

00:24:49.580 --> 00:24:51.212 So we just think about this

NOTE Confidence: 0.8580042

00:24:51.212 --> 00:24:52.300 a little bit conceptually.

NOTE Confidence: 0.8580042

00:24:52.300 --> 00:24:53.812 What this tells us is that

NOTE Confidence: 0.8580042

48

00:24:53.812 --> 00:24:55.560 when the animal is not running,

NOTE Confidence: 0.8580042

00:24:55.560 --> 00:24:57.464 sort this big pink bar of quiescence.

NOTE Confidence: 0.8580042

00:24:57.470 --> 00:24:59.198 You actually have some periods where

NOTE Confidence: 0.8580042

00:24:59.198 --> 00:25:01.148 where the animals whiskey or work where

NOTE Confidence: 0.8580042

00:25:01.148 --> 00:25:02.636 this facial motion energy is high,

NOTE Confidence: 0.8580042

00:25:02.640 --> 00:25:04.272 and then you also have some

NOTE Confidence: 0.8580042

00:25:04.272 --> 00:25:05.360 periods where it's slow,

NOTE Confidence: 0.8580042

00:25:05.360 --> 00:25:07.775 so you can get very big fluctuations

NOTE Confidence: 0.8580042

00:25:07.775 --> 00:25:09.524 in facial movement even when

NOTE Confidence: 0.8580042

00:25:09.524 --> 00:25:11.139 the animal is not running.

NOTE Confidence: 0.8580042

00:25:11.140 --> 00:25:13.651 You then look there with the far right for

NOTE Confidence: 0.8580042

00:25:13.651 --> 00:25:16.178 the periods where the animal is running.

NOTE Confidence: 0.8580042

00:25:16.180 --> 00:25:18.378 Every time that the animal is running

NOTE Confidence: 0.8580042

00:25:18.378 --> 00:25:20.280 for a sustained period of time,

NOTE Confidence: 0.8580042

00:25:20.280 --> 00:25:21.536 the facial motion energy,

NOTE Confidence: 0.8580042

00:25:21.536 --> 00:25:23.106 the facial movement is high,

NOTE Confidence: 0.8580042

00:25:23.110 --> 00:25:25.175 and so this suggests sort of a

NOTE Confidence: 0.8580042

00:25:25.175 --> 00:25:26.580 serial progression of arousal,

NOTE Confidence: 0.8580042

00:25:26.580 --> 00:25:28.561 which is that first you have like

NOTE Confidence: 0.8580042

00:25:28.561 --> 00:25:30.359 quiescence and no facial movement.

NOTE Confidence: 0.8580042

00:25:30.360 --> 00:25:31.935 Then the animal starts having

NOTE Confidence: 0.8580042

00:25:31.935 --> 00:25:32.880 some facial movement.

NOTE Confidence: 0.8580042

00:25:32.880 --> 00:25:34.770 They can go back and forth,

NOTE Confidence: 0.8580042

00:25:34.770 --> 00:25:36.648 and then at some point the

NOTE Confidence: 0.8580042

00:25:36.648 --> 00:25:38.230 animal might start to run.

NOTE Confidence: 0.8580042

00:25:38.230 --> 00:25:39.175 Whenever it runs,

NOTE Confidence: 0.8580042

00:25:39.175 --> 00:25:40.120 it's always whisking,

NOTE Confidence: 0.8580042

00:25:40.120 --> 00:25:42.488 so you've got this sort of three stage

NOTE Confidence: 0.8580042

00:25:42.488 --> 00:25:44.470 process of like total quiescence.

NOTE Confidence: 0.8580042

00:25:44.470 --> 00:25:46.440 Facial movement without running and

NOTE Confidence: 0.8580042

00:25:46.440 --> 00:25:48.759 then facial movement with running and

NOTE Confidence: 0.8580042

00:25:48.759 --> 00:25:50.761 we think that that represents a sort

NOTE Confidence: 0.8580042

00:25:50.761 --> 00:25:53.220 of serial progression of level of arousal.

NOTE Confidence: 0.84202695

00:25:55.800 --> 00:25:58.390 So what I'm showing you here then,

NOTE Confidence: 0.84202695

00:25:58.390 --> 00:26:00.568 is sort of the average fluorescence

NOTE Confidence: 0.84202695

00:26:00.568 --> 00:26:03.137 signals in the in the two indicators

NOTE Confidence: 0.84202695

00:26:03.137 --> 00:26:05.231 that I told you about divided

NOTE Confidence: 0.84202695

00:26:05.231 --> 00:26:07.638 or actually really in this case,

NOTE Confidence: 0.84202695

00:26:07.640 --> 00:26:09.926 subtracting the period of sustained high

NOTE Confidence: 0.84202695

00:26:09.926 --> 00:26:12.079 versus period of sustained load data,

NOTE Confidence: 0.84202695

00:26:12.080 --> 00:26:14.616 and so we just take the top row

NOTE Confidence: 0.84202695

00:26:14.616 --> 00:26:17.430 first here and So what we see

NOTE Confidence: 0.84202695

00:26:17.430 --> 00:26:19.110 for this cholinergic indicator,

NOTE Confidence: 0.84202695

00:26:19.110 --> 00:26:21.630 the AC H 3.0 when when you subtract

NOTE Confidence: 0.84202695

00:26:21.630 --> 00:26:24.058 high facial movement versus low facial

NOTE Confidence: 0.84202695

00:26:24.058 --> 00:26:26.218 movement you get really bright.

NOTE Confidence: 0.84202695

00:26:26.220 --> 00:26:27.876 Red signal across pretty much the

NOTE Confidence: 0.84202695

00:26:27.876 --> 00:26:29.666 whole cortex telling us that there's

NOTE Confidence: 0.84202695

00:26:29.666 --> 00:26:31.241 a lot more acetylcholine released

NOTE Confidence: 0.84202695

00:26:31.241 --> 00:26:32.902 during high facial movements than

NOTE Confidence: 0.84202695

00:26:32.902 --> 00:26:34.226 than low facial movements.

NOTE Confidence: 0.84202695

00:26:34.230 --> 00:26:36.379 So so there's a big difference there.

NOTE Confidence: 0.84202695

00:26:36.380 --> 00:26:38.536 It goes up when you look though,

NOTE Confidence: 0.84202695

00:26:38.540 --> 00:26:40.080 between transitions between no locomotion,

NOTE Confidence: 0.84202695

00:26:40.080 --> 00:26:41.620 locomotion, it's still all red.

NOTE Confidence: 0.84202695

00:26:41.620 --> 00:26:42.544 You know it,

NOTE Confidence: 0.84202695

00:26:42.544 --> 00:26:44.700 but it's a very it's much smaller,

NOTE Confidence: 0.84202695

00:26:44.700 --> 00:26:46.368 so there's a big increase in

NOTE Confidence: 0.84202695

00:26:46.368 --> 00:26:47.887 acetylcholine release when the animal

NOTE Confidence: 0.84202695

00:26:47.887 --> 00:26:49.319 starts having facial movements.

NOTE Confidence: 0.84202695

00:26:49.320 --> 00:26:51.756 And then there's a very small additional

NOTE Confidence: 0.84202695

00:26:51.756 --> 00:26:54.190 increase when the animal starts running.

NOTE Confidence: 0.84202695

00:26:54.190 --> 00:26:57.358 Then look at the bottom row for our campus.

00:26:57.360 --> 00:26:59.120 The calcium indicators for the

00:26:59.120 --> 00:27:00.528 readout of cortical activity.

00:27:00.530 --> 00:27:02.290 It's a bit the opposite,

00:27:02.290 --> 00:27:04.050 so when the animal whisks,

00:27:04.050 --> 00:27:05.810 there's a modest increase in

00:27:05.810 --> 00:27:07.570 the amount of neural activity,

00:27:07.570 --> 00:27:09.382 but there's a much bigger increase

00:27:09.382 --> 00:27:11.477 in the amount of cortical activity

00:27:11.477 --> 00:27:13.547 when the animal starts running,

00:27:13.550 --> 00:27:15.412 and so this is already starting to

00:27:15.412 --> 00:27:17.575 give us a sense that acetylcholine

00:27:17.575 --> 00:27:19.750 and cortical activity are not

00:27:19.750 --> 00:27:21.649 perfectly coupled with each other,

00:27:21.650 --> 00:27:24.338 and might be signaling different aspects of.

00:27:24.340 --> 00:27:26.910 Behavior.

NOTE Confidence: 0.84202695

00:27:26.910 --> 00:27:28.734 And actually so all of this data just

NOTE Confidence: 0.84202695

00:27:28.734 --> 00:27:30.518 to point out is is described in A

NOTE Confidence: 0.84202695

00:27:30.518 --> 00:27:32.312 in a manuscript by sweat and Andrew

NOTE Confidence: 0.84202695

00:27:32.312 --> 00:27:33.797 that's currently on by archive.

NOTE Confidence: 0.84202695

00:27:33.800 --> 00:27:35.515 If people are interested in more details.

NOTE Confidence: 0.8295353

00:27:37.780 --> 00:27:40.588 The one other little thing I'll put in here,

NOTE Confidence: 0.8295353

00:27:40.590 --> 00:27:42.767 I'm just going to mention this briefly.

NOTE Confidence: 0.8295353

00:27:42.770 --> 00:27:44.636 I'm not going too much detail,

NOTE Confidence: 0.8295353

00:27:44.640 --> 00:27:46.542 but at the same time we're

NOTE Confidence: 0.8295353

00:27:46.542 --> 00:27:48.080 doing all this image in.

NOTE Confidence: 0.8295353

00:27:48.080 --> 00:27:50.257 We have an electrode placed in cortex,

NOTE Confidence: 0.8295353

00:27:50.260 --> 00:27:52.198 which essentially gives us an Electro

NOTE Confidence: 0.8295353

00:27:52.198 --> 00:27:54.628 cortical gram or or E kog written here.

NOTE Confidence: 0.8295353

00:27:54.630 --> 00:27:56.814 This is again the sort of local

NOTE Confidence: 0.8295353

00:27:56.814 --> 00:27:57.750 field potential dynamics,

NOTE Confidence: 0.8295353

00:27:57.750 --> 00:27:58.683 the electrical signaling

NOTE Confidence: 0.8295353

00:27:58.683 --> 00:28:00.238 going on in the cortex,

NOTE Confidence: 0.8295353

00:28:00.240 --> 00:28:02.116 and what we see when you also

NOTE Confidence: 0.8295353

00:28:02.116 --> 00:28:04.298 look at low versus high arousal,

NOTE Confidence: 0.8295353

00:28:04.300 --> 00:28:05.865 whether it's facial movement or

NOTE Confidence: 0.8295353

00:28:05.865 --> 00:28:07.430 locomotion is something that's been

NOTE Confidence: 0.8295353

00:28:07.480 --> 00:28:09.070 described for decades and decades.

NOTE Confidence: 0.8295353

00:28:09.070 --> 00:28:11.518 Which is that the high frequency

NOTE Confidence: 0.8295353

00:28:11.518 --> 00:28:13.150 activity high frequency electrical

NOTE Confidence: 0.8295353

00:28:13.218 --> 00:28:15.521 activity goes up when the animal is

NOTE Confidence: 0.8295353

00:28:15.521 --> 00:28:17.267 higher aroused and the amplitude

NOTE Confidence: 0.8295353

00:28:17.267 --> 00:28:19.349 goes down and this has been

NOTE Confidence: 0.8295353

00:28:19.349 --> 00:28:21.510 interpreted for ages ascential E as

NOTE Confidence: 0.8295353

00:28:21.510 --> 00:28:23.335 local decorrelation of the network.

NOTE Confidence: 0.8295353

00:28:23.340 --> 00:28:25.734 So it basically means that neurons that

NOTE Confidence: 0.8295353

00:28:25.734 --> 00:28:28.801 are near each other in a local network

NOTE Confidence: 0.8295353

00:28:28.801 --> 00:28:30.771 or actually becoming less correlated

NOTE Confidence: 0.8295353

00:28:30.838 --> 00:28:33.225 with each other when arousal goes up.

NOTE Confidence: 0.8295353

00:28:33.230 --> 00:28:35.785 So just bear that fact in mind.

NOTE Confidence: 0.8295353

00:28:35.790 --> 00:28:36.921 It's not critical,

NOTE Confidence: 0.8295353

00:28:36.921 --> 00:28:40.179 but I mention it 'cause 'cause we've done it.

NOTE Confidence: 0.831442

00:28:42.200 --> 00:28:44.195 So these data are really about the

NOTE Confidence: 0.831442

00:28:44.195 --> 00:28:46.169 amplitudes of these fluorescent signals.

NOTE Confidence: 0.831442

00:28:46.170 --> 00:28:48.818 You know how does the average signal change.

NOTE Confidence: 0.831442

00:28:48.820 --> 00:28:50.428 So acetylcholine goes up.

NOTE Confidence: 0.831442

00:28:50.428 --> 00:28:52.438 Calcium goes up when the

NOTE Confidence: 0.831442

00:28:52.438 --> 00:28:54.438 animals arousal level goes up.

NOTE Confidence: 0.831442

00:28:54.440 --> 00:28:57.218 But really, the major advantage of

NOTE Confidence: 0.831442

00:28:57.218 --> 00:28:59.505 this imaging approach that we've

NOTE Confidence: 0.831442

00:28:59.505 --> 00:29:01.997 got where we can see the entire

NOTE Confidence: 0.831442

00:29:01.997 --> 00:29:04.614 cortex at one time is that we

NOTE Confidence: 0.831442

00:29:04.614 --> 00:29:06.793 can look at the coordination of

NOTE Confidence: 0.831442

00:29:06.793 --> 00:29:09.264 different areas so we can look at

NOTE Confidence: 0.831442

00:29:09.264 --> 00:29:11.840 relative changes in these signals in

NOTE Confidence: 0.831442

00:29:11.840 --> 00:29:13.640 different cortical areas overtime.

NOTE Confidence: 0.831442

00:29:13.640 --> 00:29:16.560 And you might imagine that.

NOTE Confidence: 0.831442

00:29:16.560 --> 00:29:18.276 Most of us think that behavior

NOTE Confidence: 0.831442

00:29:18.276 --> 00:29:19.870 happens because of the coordinated

NOTE Confidence: 0.831442

00:29:19.870 --> 00:29:21.805 activity of the nervous system,

NOTE Confidence: 0.831442

00:29:21.810 --> 00:29:23.450 and so if it's coordinated,

NOTE Confidence: 0.831442

00:29:23.450 --> 00:29:25.018 nervous system activity that's

NOTE Confidence: 0.831442

00:29:25.018 --> 00:29:26.978 driving behavior really coming up

NOTE Confidence: 0.831442

00:29:26.978 --> 00:29:29.416 with methods that allow us to see

NOTE Confidence: 0.831442

00:29:29.416 --> 00:29:31.036 that coordination rather than just

NOTE Confidence: 0.831442

00:29:31.036 --> 00:29:32.956 saying OK area a goes up or down.

NOTE Confidence: 0.831442

00:29:32.960 --> 00:29:34.268 It's really the interactions

NOTE Confidence: 0.831442

00:29:34.268 --> 00:29:35.576 that matter the most,

NOTE Confidence: 0.831442

00:29:35.580 --> 00:29:38.127 and so the power in part of this mysa

NOTE Confidence: 0.831442

00:29:38.127 --> 00:29:40.735 scopic imaging is that we can look at

NOTE Confidence: 0.831442

00:29:40.735 --> 00:29:42.799 the coordination of different areas,

NOTE Confidence: 0.831442

00:29:42.800 --> 00:29:44.666 so we're going to do that

NOTE Confidence: 0.831442

00:29:44.666 --> 00:29:46.570 now for these two signals.

NOTE Confidence: 0.831442

00:29:46.570 --> 00:29:48.928 Relative to changes in behavioral state.

NOTE Confidence: 0.8378851

00:29:51.440 --> 00:29:53.862 So the first thing that I'll mention

NOTE Confidence: 0.8378851

00:29:53.862 --> 00:29:56.528 is I alluded to it before when I

NOTE Confidence: 0.8378851

00:29:56.528 --> 00:29:58.556 said we could draw areas around

NOTE Confidence: 0.8378851

00:29:58.556 --> 00:30:00.974 safe motor or visual or whatever.

NOTE Confidence: 0.8378851

00:30:00.980 --> 00:30:03.878 How do we do that in a quantitative way?

NOTE Confidence: 0.8378851

00:30:03.880 --> 00:30:06.690 And how do we do it in a way that

NOTE Confidence: 0.8378851

00:30:06.775 --> 00:30:09.663 you know allows us to sort of say,

NOTE Confidence: 0.8378851

00:30:09.670 --> 00:30:11.878 OK, this area is the same area in

NOTE Confidence: 0.8378851

00:30:11.878 --> 00:30:14.177 mouse a mouse beam else whatever?

NOTE Confidence: 0.8378851

00:30:14.180 --> 00:30:15.488 It's not so different,

00:30:15.488 --> 00:30:17.450 for example then then then work

00:30:17.512 --> 00:30:19.330 in the fMRI community as well.

00:30:19.330 --> 00:30:20.278 We use an Atlas,

00:30:20.278 --> 00:30:22.584 and in this case we use an Atlas

00:30:22.584 --> 00:30:24.220 called the common coordinate

00:30:24.220 --> 00:30:25.447 framework version three,

00:30:25.450 --> 00:30:27.382 which was developed by the Allen

00:30:27.382 --> 00:30:28.670 Brain Institute in Seattle,

00:30:28.670 --> 00:30:30.966 and what they did was used a whole

00:30:30.966 --> 00:30:33.508 lot of anatomical labels and some.

00:30:33.510 --> 00:30:36.382 Fiber tracing labels to come up with an

00:30:36.382 --> 00:30:38.539 average parcellation of the mouse neocortex,

00:30:38.540 --> 00:30:39.972 and that's illustrated here.

00:30:39.972 --> 00:30:41.046 And so again,

00:30:41.050 --> 00:30:44.272 you know front is up back is is down.

NOTE Confidence: 0.8378851

00:30:44.280 --> 00:30:46.080 Since you got motor areas,

NOTE Confidence: 0.8378851

00:30:46.080 --> 00:30:48.872 you've got some at a sensory areas in

NOTE Confidence: 0.8378851

00:30:48.872 --> 00:30:51.457 the middle visual areas in the back.

NOTE Confidence: 0.8378851

00:30:51.460 --> 00:30:53.966 Auditory is quite lateral and so forth,

NOTE Confidence: 0.8378851

00:30:53.970 --> 00:30:56.357 and so the utility of such an

NOTE Confidence: 0.8378851

00:30:56.357 --> 00:30:58.568 Atlas is maybe a bit obvious

NOTE Confidence: 0.8378851

00:30:58.568 --> 00:31:00.788 given the points I just made,

NOTE Confidence: 0.8378851

00:31:00.790 --> 00:31:02.950 it allows a certain regularity

NOTE Confidence: 0.8378851

00:31:02.950 --> 00:31:03.814 across animals.

NOTE Confidence: 0.8378851

00:31:03.820 --> 00:31:08.230 Up its validity remains a little bit.

NOTE Confidence: 0.8378851

00:31:08.230 --> 00:31:08.512 Unclear,

NOTE Confidence: 0.8378851

00:31:08.512 --> 00:31:10.486 and I'm not going to talk about

NOTE Confidence: 0.8378851

00:31:10.486 --> 00:31:12.307 this in any detail other than

NOTE Confidence: 0.8378851

00:31:12.307 --> 00:31:14.101 just to mention it right now.

NOTE Confidence: 0.8378851

00:31:14.110 --> 00:31:16.078 There are certainly other ways of

NOTE Confidence: 0.8378851

00:31:16.078 --> 00:31:17.951 parcel eighting the cortex one could

NOTE Confidence: 0.8378851

00:31:17.951 --> 00:31:19.694 do it in an activity based way.

NOTE Confidence: 0.8378851

00:31:19.700 --> 00:31:21.443 You could in fact look at say

NOTE Confidence: 0.8378851

00:31:21.443 --> 00:31:23.597 OK Pixels in our movie that are

NOTE Confidence: 0.8378851

00:31:23.597 --> 00:31:25.277 most correlated with each other.

NOTE Confidence: 0.8378851

00:31:25.280 --> 00:31:25.556 Well,

NOTE Confidence: 0.8378851

00:31:25.556 --> 00:31:27.212 they belong to the same area

NOTE Confidence: 0.8378851

00:31:27.212 --> 00:31:29.639 and you could do that in a lot

NOTE Confidence: 0.8378851

00:31:29.639 --> 00:31:30.867 of different quantitative ways,

NOTE Confidence: 0.8378851

00:31:30.870 --> 00:31:32.823 but you could come up with some

NOTE Confidence: 0.8378851

00:31:32.823 --> 00:31:34.399 parcellation based on the activity.

NOTE Confidence: 0.8378851

00:31:34.400 --> 00:31:35.279 It turns out,

NOTE Confidence: 0.8378851

00:31:35.279 --> 00:31:37.037 for reasons that aren't totally clear,

NOTE Confidence: 0.8378851

00:31:37.040 --> 00:31:38.515 those kinds of functional parcellation's

NOTE Confidence: 0.8378851

00:31:38.515 --> 00:31:40.360 don't map onto these anatomical atlases.

NOTE Confidence: 0.8378851

00:31:40.360 --> 00:31:43.015 All that well and the reasons for that are,

NOTE Confidence: 0.8378851

00:31:43.020 --> 00:31:43.857 as I said,

NOTE Confidence: 0.8378851

00:31:43.857 --> 00:31:45.810 are unclear and is actually something that

NOTE Confidence: 0.8378851

00:31:45.868 --> 00:31:48.024 we're quite interested in pursuing a lot.

NOTE Confidence: 0.8378851

00:31:48.030 --> 00:31:50.095 But for the moment for convenience sake,

NOTE Confidence: 0.8378851

00:31:50.100 --> 00:31:51.570 and certainly for these data,

NOTE Confidence: 0.8378851

00:31:51.570 --> 00:31:53.348 we're just going to stick to this

NOTE Confidence: 0.8378851

00:31:53.348 --> 00:31:54.937 Allen Brain Atlas and we're going

NOTE Confidence: 0.8378851

00:31:54.937 --> 00:31:56.491 to say that area is circumscribed

NOTE Confidence: 0.8378851

00:31:56.491 --> 00:31:57.973 by these borders correspond

NOTE Confidence: 0.8378851

00:31:57.973 --> 00:31:59.537 to functionally related areas.

NOTE Confidence: 0.8591862

00:32:01.700 --> 00:32:04.121 So now we can make plots like this and

NOTE Confidence: 0.8591862

00:32:04.121 --> 00:32:06.440 you may recall a couple slides ago.

NOTE Confidence: 0.8591862

00:32:06.440 --> 00:32:08.896 I sort of showed you that running correlation

NOTE Confidence: 0.8591862

00:32:08.896 --> 00:32:11.286 between say motor and vision and so all

NOTE Confidence: 0.8591862

00:32:11.286 --> 00:32:13.240 these sort of complicated shapes are is.

NOTE Confidence: 0.8591862

00:32:13.240 --> 00:32:15.598 So if we just look at the one on

NOTE Confidence: 0.8591862

00:32:15.598 --> 00:32:18.006 the far left for the moment, right?

NOTE Confidence: 0.8591862

00:32:18.006 --> 00:32:20.288 We've got all of these cortical regions

NOTE Confidence: 0.8591862

00:32:20.288 --> 00:32:22.314 defined by the Allen Atlas on the

NOTE Confidence: 0.8591862

00:32:22.314 --> 00:32:24.490 bottom axis and also on the left axis.

NOTE Confidence: 0.8591862

00:32:24.490 --> 00:32:26.562 And so we're going to do a

NOTE Confidence: 0.8591862

00:32:26.562 --> 00:32:27.154 pairwise correlation.

NOTE Confidence: 0.8591862

00:32:27.160 --> 00:32:29.491 So every pair of areas we're just going to

NOTE Confidence: 0.8591862

00:32:29.491 --> 00:32:31.687 take the average correlation in signal.

NOTE Confidence: 0.8591862

00:32:31.690 --> 00:32:32.740 Between, you know,

NOTE Confidence: 0.8591862

00:32:32.740 --> 00:32:35.190 say motor and vision or motor and

NOTE Confidence: 0.8591862

00:32:35.266 --> 00:32:37.286 auditory or motor and sensory.

NOTE Confidence: 0.8591862

00:32:37.290 --> 00:32:39.579 So every little box in this matrix

NOTE Confidence: 0.8591862

00:32:39.579 --> 00:32:41.485 is the average correlation between

NOTE Confidence: 0.8591862

00:32:41.485 --> 00:32:43.630 a pair of cortical areas,

NOTE Confidence: 0.8591862

00:32:43.630 --> 00:32:46.241 and so you can see the entire

NOTE Confidence: 0.8591862

00:32:46.241 --> 00:32:47.360 pairwise matrix here,

NOTE Confidence: 0.8591862

00:32:47.360 --> 00:32:49.592 and we've done this now for

NOTE Confidence: 0.8591862

00:32:49.592 --> 00:32:50.708 the cholinergic signal.

NOTE Confidence: 0.8591862

00:32:50.710 --> 00:32:53.320 On the left is a stage 3.0 and our

NOTE Confidence: 0.8591862

00:32:53.320 --> 00:32:56.008 camp on the right the calcium signal

NOTE Confidence: 0.8591862

00:32:56.008 --> 00:32:58.947 and rather than show you the absolute

NOTE Confidence: 0.8591862

00:32:58.947 --> 00:33:02.020 correlations what I'm showing you is that.

NOTE Confidence: 0.8591862

00:33:02.020 --> 00:33:03.319 Difference in correlations

NOTE Confidence: 0.8591862

00:33:03.319 --> 00:33:04.618 across behavioral state.

NOTE Confidence: 0.8591862

00:33:04.620 --> 00:33:08.100 So in this case this is high facial

NOTE Confidence: 0.8591862

00:33:08.100 --> 00:33:10.914 movement minus low facial movement and

NOTE Confidence: 0.8591862

00:33:10.914 --> 00:33:14.540 the fact that pretty much all of this

NOTE Confidence: 0.8591862

00:33:14.540 --> 00:33:17.604 is red in both graphs tells you that

NOTE Confidence: 0.8591862

00:33:17.610 --> 00:33:19.770 the correlations the pairwise correlations,

NOTE Confidence: 0.8591862

00:33:19.770 --> 00:33:22.368 the sameness or the similarity in

NOTE Confidence: 0.8591862

00:33:22.368 --> 00:33:24.594 activity between two areas goes

NOTE Confidence: 0.8591862

00:33:24.594 --> 00:33:26.699 up for pretty much everything.

NOTE Confidence: 0.8591862

00:33:26.700 --> 00:33:29.250 So both acetylcholine and calcium

NOTE Confidence: 0.8591862

00:33:29.250 --> 00:33:32.225 signaling are becoming more correlated for

NOTE Confidence: 0.8591862

00:33:32.225 --> 00:33:34.993 every most pairs of areas in the cortex.

NOTE Confidence: 0.8591862

00:33:35.000 --> 00:33:37.260 When the animal starts whisking,

NOTE Confidence: 0.8591862

00:33:37.260 --> 00:33:37.630 so.

NOTE Confidence: 0.8591862

00:33:37.630 --> 00:33:38.000 Firstly,

NOTE Confidence: 0.8591862

00:33:38.000 --> 00:33:39.850 that's a little bit interesting

NOTE Confidence: 0.8591862

00:33:39.850 --> 00:33:43.184 because I just told you a moment ago

NOTE Confidence: 0.8591862

00:33:43.184 --> 00:33:44.912 that from these electrophysiological

NOTE Confidence: 0.8591862

00:33:44.912 --> 00:33:46.228 recordings that we make,

NOTE Confidence: 0.8591862

00:33:46.230 --> 00:33:48.246 that provides evidence that local circuits

NOTE Confidence: 0.8591862

00:33:48.246 --> 00:33:50.180 are actually becoming less correlated,

NOTE Confidence: 0.8591862

00:33:50.180 --> 00:33:51.975 and that's really sort of

NOTE Confidence: 0.8591862

00:33:51.975 --> 00:33:53.770 party line right for ages,

NOTE Confidence: 0.8591862

00:33:53.770 --> 00:33:55.834 everybody knows that arousal goes with

NOTE Confidence: 0.8591862

00:33:55.834 --> 00:33:57.720 reduced correlations of local circuits,

NOTE Confidence: 0.8591862

00:33:57.720 --> 00:33:59.939 and what I'm actually showing you here

NOTE Confidence: 0.8591862

00:33:59.939 --> 00:34:02.062 from these large scale imaging studies

NOTE Confidence: 0.8591862

00:34:02.062 --> 00:34:04.276 is that being circuits big networks

NOTE Confidence: 0.8591862

00:34:04.276 --> 00:34:06.645 across the whole cortex or actually

NOTE Confidence: 0.8591862

00:34:06.645 --> 00:34:08.580 becoming more correlated with arousal.

NOTE Confidence: 0.8591862

00:34:08.580 --> 00:34:11.380 And that we see that for both cholinergic

NOTE Confidence: 0.8591862

00:34:11.380 --> 00:34:13.468 signals and for for for calcium.

NOTE Confidence: 0.8591862

00:34:13.470 --> 00:34:15.564 So that's kind of cool and

NOTE Confidence: 0.8591862

00:34:15.564 --> 00:34:16.960 a little bit unexpected.

NOTE Confidence: 0.8591862

00:34:16.960 --> 00:34:18.580 But something that emerges from

NOTE Confidence: 0.8591862

00:34:18.580 --> 00:34:20.800 this from this image in modality.

NOTE Confidence: 0.8591862

00:34:20.800 --> 00:34:22.888 So this is for facial movements.

NOTE Confidence: 0.8591862

00:34:22.890 --> 00:34:26.320 Now we're going to do the same

NOTE Confidence: 0.8591862

00:34:26.320 --> 00:34:27.790 thing for locomotion.

NOTE Confidence: 0.8591862

00:34:27.790 --> 00:34:29.680 It looks different.

NOTE Confidence: 0.8591862

00:34:29.680 --> 00:34:32.102 So the calcium signal in our camp

NOTE Confidence: 0.8591862

00:34:32.102 --> 00:34:33.140 looks similar ish.

NOTE Confidence: 0.8591862

00:34:33.140 --> 00:34:35.216 I mean most things are red.

NOTE Confidence: 0.8591862

00:34:35.220 --> 00:34:36.950 It's a little less red.

NOTE Confidence: 0.8591862

00:34:36.950 --> 00:34:38.868 Sorry that the Gray boxes are those

NOTE Confidence: 0.8591862

00:34:38.868 --> 00:34:41.100 that were not significantly different,

NOTE Confidence: 0.8591862

00:34:41.100 --> 00:34:43.868 so if it has a color in it,

NOTE Confidence: 0.8591862

00:34:43.870 --> 00:34:45.600 it's significantly bigger or smaller.

NOTE Confidence: 0.8591862

00:34:45.600 --> 00:34:46.980 If it's just grey,

NOTE Confidence: 0.8591862

00:34:46.980 --> 00:34:48.705 it was non significantly different.

NOTE Confidence: 0.8591862

00:34:48.710 --> 00:34:51.815 So the calcium signal goes a little bit less,

NOTE Confidence: 0.8591862

00:34:51.820 --> 00:34:53.764 but someone but the acetylcholine goes

NOTE Confidence: 0.8591862

00:34:53.764 --> 00:34:55.630 robustly in the opposite direction.

NOTE Confidence: 0.8591862

00:34:55.630 --> 00:34:57.790 So what this is telling us is when

NOTE Confidence: 0.8591862

00:34:57.790 --> 00:34:59.743 the animal starts whisking the

NOTE Confidence: 0.8591862

00:34:59.743 --> 00:35:01.543 correlations in acetylcholine release

NOTE Confidence: 0.8591862

00:35:01.543 --> 00:35:03.739 across the cortex are going up.

NOTE Confidence: 0.8475224

00:35:03.740 --> 00:35:06.120 But suddenly when the animal starts running,

NOTE Confidence: 0.8475224

00:35:06.120 --> 00:35:08.160 the release of acetylcholine in different

NOTE Confidence: 0.8475224

00:35:08.160 --> 00:35:09.520 cortical areas completely decorrelate's.

NOTE Confidence: 0.8475224

00:35:09.520 --> 00:35:11.774 I will just say right now we

NOTE Confidence: 0.8475224

00:35:11.774 --> 00:35:13.939 really don't know what that needs.

NOTE Confidence: 0.8475224

00:35:13.940 --> 00:35:15.640 It is a purely observation.

NOTE Confidence: 0.8475224

00:35:15.640 --> 00:35:18.090 Ull point from these data were very

NOTE Confidence: 0.8475224

00:35:18.090 --> 00:35:20.199 interested in what it means and

NOTE Confidence: 0.8475224

00:35:20.199 --> 00:35:22.179 many follow up studies are being

NOTE Confidence: 0.8475224

00:35:22.179 --> 00:35:24.138 being carried out in our labs.

NOTE Confidence: 0.8475224

00:35:24.140 --> 00:35:26.196 And it's also in others to sort of

NOTE Confidence: 0.8475224

00:35:26.196 --> 00:35:28.219 think about mechanistic relationships,

NOTE Confidence: 0.8475224

00:35:28.220 --> 00:35:30.124 but at the moment I mean this

NOTE Confidence: 0.8475224

00:35:30.124 --> 00:35:32.320 is this is quite striking and

NOTE Confidence: 0.8475224

00:35:32.320 --> 00:35:34.068 and again emphasizes that.

NOTE Confidence: 0.8475224

00:35:34.070 --> 00:35:36.050 Acetylcholine is not sort of a

NOTE Confidence: 0.8475224

00:35:36.050 --> 00:35:37.890 really simplistic signal of arousal,

NOTE Confidence: 0.8475224

00:35:37.890 --> 00:35:39.630 as really interesting dynamics that

NOTE Confidence: 0.8475224

00:35:39.630 --> 00:35:41.758 seem to be differentially coupled to

NOTE Confidence: 0.8475224

00:35:41.758 --> 00:35:43.438 different kinds of behavioral states.

NOTE Confidence: 0.8475224

00:35:43.440 --> 00:35:45.534 It also tells us that calcium

NOTE Confidence: 0.8475224

00:35:45.534 --> 00:35:46.581 signaling acetylcholine signaling

NOTE Confidence: 0.8475224

00:35:46.581 --> 00:35:47.950 don't always go together,

NOTE Confidence: 0.8475224

00:35:47.950 --> 00:35:49.930 and so the relationship there is

NOTE Confidence: 0.8475224

00:35:49.930 --> 00:35:52.110 something that we're very interested in.

NOTE Confidence: 0.837383539473684

00:35:54.140 --> 00:35:56.660 Alright, so. This is a summary

NOTE Confidence: 0.837383539473684

00:35:56.660 --> 00:35:59.720 figure than of what we've sort of

NOTE Confidence: 0.837383539473684

00:35:59.720 --> 00:36:02.300 extracted from all of that data.

NOTE Confidence: 0.837383539473684

00:36:02.300 --> 00:36:05.259 So if I was to give you any sort of take

NOTE Confidence: 0.837383539473684

00:36:05.259 --> 00:36:08.291 home that was divorced from the from the

NOTE Confidence: 0.837383539473684

00:36:08.291 --> 00:36:11.395 details that it might be something like this,

NOTE Confidence: 0.837383539473684

00:36:11.400 --> 00:36:13.416 so we envision, right that arousal,

NOTE Confidence: 0.837383539473684

00:36:13.420 --> 00:36:14.434 whatever that means,

NOTE Confidence: 0.837383539473684

00:36:14.434 --> 00:36:15.446 operationally defined, again,

NOTE Confidence: 0.837383539473684

00:36:15.446 --> 00:36:16.790 not not really conceptually,

NOTE Confidence: 0.837383539473684

00:36:16.790 --> 00:36:19.486 goes up in some kind of monotonic fashion,

NOTE Confidence: 0.837383539473684

00:36:19.490 --> 00:36:21.392 an it operationally goes from the

NOTE Confidence: 0.837383539473684

00:36:21.392 --> 00:36:23.074 animal really just sitting there

NOTE Confidence: 0.837383539473684

00:36:23.074 --> 00:36:24.879 completely passively to the animal,

NOTE Confidence: 0.837383539473684

00:36:24.880 --> 00:36:27.239 beginning to whisk to the animal whisking,

NOTE Confidence: 0.837383539473684

00:36:27.240 --> 00:36:28.359 and also running.

NOTE Confidence: 0.837383539473684

00:36:28.359 --> 00:36:29.478 On a wheel,

NOTE Confidence: 0.837383539473684

00:36:29.480 --> 00:36:31.832 and that that transition seems to go

NOTE Confidence: 0.837383539473684

00:36:31.832 --> 00:36:34.537 with an overall increase in the amount

NOTE Confidence: 0.837383539473684

00:36:34.537 --> 00:36:36.165 of acetylcholine that's released

NOTE Confidence: 0.837383539473684

00:36:36.165 --> 00:36:39.204 and the overall activity of the of

NOTE Confidence: 0.837383539473684

00:36:39.204 --> 00:36:40.928 the cortical networks themselves.

NOTE Confidence: 0.837383539473684

00:36:40.930 --> 00:36:42.402 If we then though,

NOTE Confidence: 0.837383539473684

00:36:42.402 --> 00:36:44.242 look at the correlations between

NOTE Confidence: 0.837383539473684

00:36:44.242 --> 00:36:45.838 areas within the cortex,

NOTE Confidence: 0.837383539473684

00:36:45.840 --> 00:36:48.102 we see that local cortical circuit

NOTE Confidence: 0.837383539473684

00:36:48.102 --> 00:36:50.000 correlations tend to go down.

NOTE Confidence: 0.837383539473684

00:36:50.000 --> 00:36:51.890 That's from the electrophysiological data,

NOTE Confidence: 0.837383539473684

00:36:51.890 --> 00:36:52.646 and many,

NOTE Confidence: 0.837383539473684

00:36:52.646 --> 00:36:53.780 many other labs,

NOTE Confidence: 0.837383539473684

00:36:53.780 --> 00:36:56.042 but the large scale cortical network

NOTE Confidence: 0.837383539473684

00:36:56.042 --> 00:36:57.173 correlations go up.

NOTE Confidence: 0.837383539473684

00:36:57.180 --> 00:36:59.070 That's that's the Arkham correlations,

NOTE Confidence: 0.837383539473684

00:36:59.070 --> 00:37:01.950 but the acetylcholine follows this very

00:37:01.950 --> 00:37:03.870 interesting non monotonic relationship

00:37:03.936 --> 00:37:06.218 where correlations first go up and then

00:37:06.218 --> 00:37:08.931 go down again as the animal progresses

00:37:08.931 --> 00:37:11.016 through this this arousal continuum.

00:37:11.020 --> 00:37:13.774 So this is sort of the take home now.

00:37:13.780 --> 00:37:14.396 I mean,

00:37:14.396 --> 00:37:15.320 obviously this is.

00:37:15.320 --> 00:37:17.568 This is a little bit unsatisfying in the

00:37:17.568 --> 00:37:19.619 sense that we don't necessarily know,

00:37:19.620 --> 00:37:21.769 at a mechanistic level what this means.

00:37:21.770 --> 00:37:22.354 But really,

00:37:22.354 --> 00:37:22.938 I mean,

00:37:22.938 --> 00:37:24.690 I would emphasize that this is

00:37:24.756 --> 00:37:26.580 kind of the cutting edge of

00:37:26.580 --> 00:37:28.210 preclinical work at this point,

00:37:28.210 --> 00:37:31.126 and so This Is Us starting to lay the

NOTE Confidence: 0.837383539473684

00:37:31.126 --> 00:37:32.923 groundwork for understanding more

NOTE Confidence: 0.837383539473684

00:37:32.923 --> 00:37:35.719 about about how these signals interact.

NOTE Confidence: 0.837383539473684

00:37:35.720 --> 00:37:36.117 Alright,

NOTE Confidence: 0.837383539473684

00:37:36.117 --> 00:37:38.896 so now I'm going to switch briefly

NOTE Confidence: 0.837383539473684

00:37:38.896 --> 00:37:41.512 to one more methodological riff

NOTE Confidence: 0.837383539473684

00:37:41.512 --> 00:37:43.828 on this widefield imaging.

NOTE Confidence: 0.837383539473684

00:37:43.830 --> 00:37:46.091 And I've alluded to local circuits and

NOTE Confidence: 0.837383539473684

00:37:46.091 --> 00:37:47.868 individual neurons within a small region,

NOTE Confidence: 0.837383539473684

00:37:47.870 --> 00:37:49.676 and that they might be doing

NOTE Confidence: 0.837383539473684

00:37:49.676 --> 00:37:51.197 interesting things and then obviously

NOTE Confidence: 0.837383539473684

00:37:51.197 --> 00:37:53.261 I've shown you a lot of data for

NOTE Confidence: 0.837383539473684

00:37:53.261 --> 00:37:55.028 large scale circuit organization.

NOTE Confidence: 0.837383539473684

00:37:55.030 --> 00:37:55.289 Well,

NOTE Confidence: 0.837383539473684

00:37:55.289 --> 00:37:57.102 what if you really wanted to get

NOTE Confidence: 0.837383539473684

00:37:57.102 --> 00:37:59.516 a nice readout of both of those

NOTE Confidence: 0.837383539473684

00:37:59.516 --> 00:38:00.617 two things simultaneously?

NOTE Confidence: 0.837383539473684

00:38:00.620 --> 00:38:02.797 So what are single cells doing water,

NOTE Confidence: 0.837383539473684

00:38:02.800 --> 00:38:04.755 large networks doing and how

NOTE Confidence: 0.837383539473684

00:38:04.755 --> 00:38:05.928 do they interact?

NOTE Confidence: 0.837383539473684

00:38:05.930 --> 00:38:08.498 So Dan Barson is an MD PhD student

NOTE Confidence: 0.837383539473684

00:38:08.498 --> 00:38:10.946 who is in my lab and also Co.

NOTE Confidence: 0.837383539473684

00:38:10.950 --> 00:38:12.924 Advised by Mike Rare and Dan and

NOTE Confidence: 0.837383539473684

00:38:12.924 --> 00:38:15.011 Alijah Modi and in my prayers lab

NOTE Confidence: 0.837383539473684

00:38:15.011 --> 00:38:17.191 came up with this approach where we

NOTE Confidence: 0.837383539473684

00:38:17.191 --> 00:38:18.956 combine this widefield mysa scopic

NOTE Confidence: 0.837383539473684

00:38:18.956 --> 00:38:21.028 imaging that I've been showing you

NOTE Confidence: 0.837383539473684

00:38:21.028 --> 00:38:23.331 with what's a little bit my labs

NOTE Confidence: 0.837383539473684

00:38:23.331 --> 00:38:25.750 with bread and butter which is 2

NOTE Confidence: 0.837383539473684

00:38:25.750 --> 00:38:27.952 photon imaging and I'm not going to

NOTE Confidence: 0.837383539473684

00:38:27.952 --> 00:38:30.732 go into a lot of detail of what that means.

NOTE Confidence: 0.837383539473684

00:38:30.732 --> 00:38:32.616 If you're not familiar with it,

NOTE Confidence: 0.837383539473684

00:38:32.620 --> 00:38:34.190 but essentially two photon imaging

NOTE Confidence: 0.837383539473684

00:38:34.190 --> 00:38:35.446 is cellularly resolved imaging,

NOTE Confidence: 0.837383539473684

00:38:35.450 --> 00:38:37.100 although over a much smaller.

NOTE Confidence: 0.837383539473684

00:38:37.100 --> 00:38:38.870 Field of view and you'll see

NOTE Confidence: 0.837383539473684

00:38:38.870 --> 00:38:40.610 that in just a second.

NOTE Confidence: 0.837383539473684

00:38:40.610 --> 00:38:42.549 So in some sense this is mashing

NOTE Confidence: 0.837383539473684

00:38:42.549 --> 00:38:44.120 up two different microscopes,

NOTE Confidence: 0.837383539473684

00:38:44.120 --> 00:38:46.150 Amy's a scope and a two photon

NOTE Confidence: 0.837383539473684

00:38:46.150 --> 00:38:48.120 microscope that we sort of just

NOTE Confidence: 0.837383539473684

00:38:48.120 --> 00:38:49.855 slammed together on optical table,

NOTE Confidence: 0.8066031

00:38:49.860 --> 00:38:52.393 made some tweaks to it, and allows us

NOTE Confidence: 0.8066031

00:38:52.393 --> 00:38:54.960 to use both modalities at the same time.

NOTE Confidence: 0.8066031

00:38:54.960 --> 00:38:57.200 And it basically looks something like this.

NOTE Confidence: 0.8066031

00:38:57.200 --> 00:38:59.873 So on the left these are kinds of images

NOTE Confidence: 0.8066031

00:38:59.873 --> 00:39:02.413 that I've been showing you now for a

00:39:02.413 --> 00:39:05.113 few minutes and on the right these are

00:39:05.113 --> 00:39:07.650 two photon images, so this Gray box.

00:39:07.650 --> 00:39:09.930 This sort of field of view.

00:39:09.930 --> 00:39:12.666 Is the entire T of a tiny little box,

00:39:12.670 --> 00:39:14.488 shown here in the dotted lines,

00:39:14.490 --> 00:39:17.100 so this whole big box here is really just

00:39:17.100 --> 00:39:19.957 a tiny little bit of all of the cortex,

00:39:19.960 --> 00:39:21.455 and these faint white circles

00:39:21.455 --> 00:39:23.310 or blobs that you see here.

00:39:23.310 --> 00:39:25.669 Each one of those is a single

00:39:25.669 --> 00:39:27.310 neuron in the cortex.

00:39:27.310 --> 00:39:29.248 So maybe I'll play the movie.

00:39:29.250 --> 00:39:30.039 And So what?

00:39:30.039 --> 00:39:31.880 You can appreciate now is these data

00:39:31.940 --> 00:39:33.768 are being acquired simultaneously,

00:39:33.770 --> 00:39:35.390 so we are now watching.

NOTE Confidence: 0.8066031

00:39:35.390 --> 00:39:37.364 So every time one of these

NOTE Confidence: 0.8066031

00:39:37.364 --> 00:39:38.940 little blobs here lights up,

NOTE Confidence: 0.8066031

00:39:38.940 --> 00:39:40.974 that's that neuron firing action potentials

NOTE Confidence: 0.8066031

00:39:40.974 --> 00:39:43.779 and every time an area over here lights up,

NOTE Confidence: 0.8066031

00:39:43.780 --> 00:39:45.718 that's that cortical region being active.

NOTE Confidence: 0.8066031

00:39:45.720 --> 00:39:48.627 And so this approach now allows us to say,

NOTE Confidence: 0.8066031

00:39:48.630 --> 00:39:51.206 well, OK, we in this neuron is active.

NOTE Confidence: 0.8066031

00:39:51.210 --> 00:39:52.830 What cortical regions are active,

NOTE Confidence: 0.8066031

00:39:52.830 --> 00:39:54.762 and vice versa when a particular

NOTE Confidence: 0.8066031

00:39:54.762 --> 00:39:55.728 region is active,

NOTE Confidence: 0.8066031

00:39:55.730 --> 00:39:57.450 even if it's far away?

NOTE Confidence: 0.8066031

00:39:57.450 --> 00:39:58.722 From where we're imaging

NOTE Confidence: 0.8066031

00:39:58.722 --> 00:40:00.312 these cells doesn't have any.

NOTE Confidence: 0.8066031

00:40:00.320 --> 00:40:02.072 Impact on the output of this

NOTE Confidence: 0.8066031

00:40:02.072 --> 00:40:03.720 single neuron and so really,

NOTE Confidence: 0.8066031

00:40:03.720 --> 00:40:04.214 you know,

NOTE Confidence: 0.8066031

00:40:04.214 --> 00:40:06.190 we feel like this is a little bit

NOTE Confidence: 0.8066031

00:40:06.253 --> 00:40:08.359 of a groundbreaking approach to try

NOTE Confidence: 0.8066031

00:40:08.359 --> 00:40:10.455 to relate multiple scales of neural

NOTE Confidence: 0.8066031

00:40:10.455 --> 00:40:12.351 activity really from the single cell

NOTE Confidence: 0.8066031

00:40:12.351 --> 00:40:15.290 level up to large scale networks an.

NOTE Confidence: 0.8066031

00:40:15.290 --> 00:40:17.236 As one slide to sort of illustrate

NOTE Confidence: 0.8066031

00:40:17.236 --> 00:40:18.920 what we can do with that,

NOTE Confidence: 0.8066031

00:40:18.920 --> 00:40:20.866 I'll just walk you through this example.

NOTE Confidence: 0.8066031

00:40:20.870 --> 00:40:22.270 So this blue trace here.

NOTE Confidence: 0.8066031

00:40:22.270 --> 00:40:23.938 This is just the time series,

NOTE Confidence: 0.8066031

00:40:23.940 --> 00:40:25.608 the activity of a single neuron.

NOTE Confidence: 0.8066031

00:40:25.610 --> 00:40:27.278 So we just take the fluorescence

NOTE Confidence: 0.8066031

00:40:27.278 --> 00:40:28.112 from one neuron.

NOTE Confidence: 0.8066031

00:40:28.120 --> 00:40:30.360 We plotted overtime and you can see it.

NOTE Confidence: 0.8066031

78

00:40:30.360 --> 00:40:32.046 It goes up in these little

NOTE Confidence: 0.8066031

00:40:32.046 --> 00:40:33.699 spiky things and then is flat,

NOTE Confidence: 0.8066031

00:40:33.700 --> 00:40:35.548 and so everyone of these little transients

NOTE Confidence: 0.8066031

00:40:35.548 --> 00:40:37.887 is when that cell fires an action potential.

NOTE Confidence: 0.8066031

00:40:37.890 --> 00:40:40.260 Or maybe a few action potentials.

NOTE Confidence: 0.8066031

00:40:40.260 --> 00:40:42.108 We can then take that Nisa

NOTE Confidence: 0.8066031

00:40:42.108 --> 00:40:43.032 Scopic movie right,

NOTE Confidence: 0.8066031

00:40:43.040 --> 00:40:44.276 which is a movie.

NOTE Confidence: 0.8066031

00:40:44.276 --> 00:40:46.130 It's a whole bunch of frames,

NOTE Confidence: 0.8066031

00:40:46.130 --> 00:40:48.014 and functionally you can take every

NOTE Confidence: 0.8066031

00:40:48.014 --> 00:40:49.885 frame from that movie that corresponds

NOTE Confidence: 0.8066031

00:40:49.885 --> 00:40:52.481 in time to one where one of these spikes

NOTE Confidence: 0.8066031

00:40:52.481 --> 00:40:54.467 are and you average those together.

NOTE Confidence: 0.8066031

00:40:54.470 --> 00:40:56.591 You only average the ones that are

NOTE Confidence: 0.8066031

00:40:56.591 --> 00:40:58.488 present when this cell is spiking,

NOTE Confidence: 0.8066031

00:40:58.490 --> 00:41:01.019 and that gives you this image here and we

NOTE Confidence: 0.8066031

00:41:01.019 --> 00:41:03.438 call this a an event triggered average.

NOTE Confidence: 0.8066031

00:41:03.440 --> 00:41:05.533 We call it a cell centered network

NOTE Confidence: 0.8066031

00:41:05.533 --> 00:41:08.415 and what it is is the areas across the

NOTE Confidence: 0.8066031

00:41:08.415 --> 00:41:10.538 cortex again front and front is up.

NOTE Confidence: 0.8066031

00:41:10.540 --> 00:41:11.413 Back is down.

NOTE Confidence: 0.8066031

00:41:11.413 --> 00:41:13.450 These are the areas of the cortex

NOTE Confidence: 0.8066031

00:41:13.512 --> 00:41:15.427 that are strongly coactive or

NOTE Confidence: 0.8066031

00:41:15.427 --> 00:41:17.342 correlated with this one neuron,

NOTE Confidence: 0.8066031

00:41:17.350 --> 00:41:19.331 and so you can imagine that you

NOTE Confidence: 0.8066031

00:41:19.331 --> 00:41:21.802 could do it for every neuron in your

NOTE Confidence: 0.8066031

00:41:21.802 --> 00:41:24.585 field of view and what it turns out

NOTE Confidence: 0.8066031

00:41:24.585 --> 00:41:26.919 is that individual neurons have very

NOTE Confidence: 0.8066031

00:41:26.919 --> 00:41:29.035 different SCMS telling us that the

NOTE Confidence: 0.8066031

00:41:29.035 --> 00:41:30.760 long range connectivity of single

NOTE Confidence: 0.8482701

00:41:30.827 --> 00:41:33.228 cells varies a lot, even for two cells

NOTE Confidence: 0.8482701

00:41:33.228 --> 00:41:35.610 which are right next to each other,

NOTE Confidence: 0.8482701

00:41:35.610 --> 00:41:37.440 and so we're using this approach

NOTE Confidence: 0.8482701

00:41:37.440 --> 00:41:38.660 to learn something about

NOTE Confidence: 0.8482701

00:41:38.716 --> 00:41:40.586 connectivity between big and small,

NOTE Confidence: 0.8482701

00:41:40.590 --> 00:41:42.935 and just to bring in some of

NOTE Confidence: 0.8482701

00:41:42.935 --> 00:41:44.360 the behavioral state data.

NOTE Confidence: 0.8482701

00:41:44.360 --> 00:41:46.736 It also turns out that those networks are

NOTE Confidence: 0.8482701

00:41:46.736 --> 00:41:49.109 dynamic as a functional behavioral state,

NOTE Confidence: 0.8482701

00:41:49.110 --> 00:41:51.476 and here these are just two examples.

NOTE Confidence: 0.8482701

00:41:51.480 --> 00:41:53.384 Top is 1 example of autumn is

NOTE Confidence: 0.8482701

00:41:53.384 --> 00:41:55.031 another where we calculated this

NOTE Confidence: 0.8482701

00:41:55.031 --> 00:41:57.335 sort of average network for two

NOTE Confidence: 0.8482701

00:41:57.335 --> 00:41:58.940 different neurons divided into,

NOTE Confidence: 0.8482701

00:41:58.940 --> 00:42:00.344 say, whisking in quiescence.

NOTE Confidence: 0.8482701

00:42:00.344 --> 00:42:03.148 And what you'll see is the fact that

NOTE Confidence: 0.8482701

00:42:03.148 --> 00:42:05.652 the left image and the right image look

00:42:05.720 --> 00:42:07.754 different tells us that the coupling

00:42:07.754 --> 00:42:10.598 of each of these two neurons to the

00:42:10.598 --> 00:42:12.458 large scale cortical network differs

00:42:12.458 --> 00:42:14.666 whether the animal is whisking or not.

00:42:14.670 --> 00:42:16.250 And here on the right,

00:42:16.250 --> 00:42:18.532 these are just the correlations of these

00:42:18.532 --> 00:42:20.989 two Maps for a whole bunch of cells.

00:42:20.990 --> 00:42:23.446 So if the left and the right were

00:42:23.446 --> 00:42:25.494 exactly the same, you get a one,

00:42:25.494 --> 00:42:27.030 and if they were sort of

00:42:27.103 --> 00:42:29.208 totally unrelated to each other,

00:42:29.210 --> 00:42:30.290 you get a zero.

00:42:30.290 --> 00:42:32.626 And So what you see is that for

00:42:32.626 --> 00:42:34.546 all the neurons in cortex it

00:42:34.546 --> 00:42:36.469 kind of spans that range,

00:42:36.470 --> 00:42:38.366 and so is the animal transitions

00:42:38.366 --> 00:42:39.314 across behavioral states.

00:42:39.320 --> 00:42:41.180 Some cells really don't care their

00:42:41.180 --> 00:42:42.790 large scale connectivity doesn't change,

00:42:42.790 --> 00:42:44.425 and other neurons completely reorganized

00:42:44.425 --> 00:42:45.733 their large scale connectivity.

00:42:45.740 --> 00:42:48.038 As a function of the animals

00:42:48.038 --> 00:42:48.804 behavioral state,

00:42:48.810 --> 00:42:49.632 so again,

00:42:49.632 --> 00:42:52.098 really providing this this cool evidence

00:42:52.098 --> 00:42:54.189 that connectivity is not only anatomy.

00:42:54.190 --> 00:42:56.758 Connectivity is very much a functional

00:42:56.758 --> 00:42:59.199 property of what the brain happens

00:42:59.199 --> 00:43:02.250 to be doing it at any moment to time.

00:43:02.250 --> 00:43:05.330 And the last thing I will say

00:43:05.330 --> 00:43:07.280 about all of this.

NOTE Confidence: 0.8482701

00:43:07.280 --> 00:43:09.180 Is that because these indicators

NOTE Confidence: 0.8482701

00:43:09.180 --> 00:43:10.320 are genetically encoded?

NOTE Confidence: 0.8482701

00:43:10.320 --> 00:43:12.763 We can express them in pretty much

NOTE Confidence: 0.8482701

00:43:12.763 --> 00:43:15.260 whatever cell type you're interested in,

NOTE Confidence: 0.8482701

00:43:15.260 --> 00:43:17.920 so if you want to say OK,

NOTE Confidence: 0.8482701

00:43:17.920 --> 00:43:20.200 these are all for excitatory neurons.

NOTE Confidence: 0.8482701

00:43:20.200 --> 00:43:22.979 These are kind of the connectivity Maps

NOTE Confidence: 0.8482701

00:43:22.979 --> 00:43:25.139 for excitatory neurons in the cortex.

NOTE Confidence: 0.8482701

00:43:25.140 --> 00:43:25.520 Well,

NOTE Confidence: 0.8482701

00:43:25.520 --> 00:43:27.800 what if you're interested in interneurons?

NOTE Confidence: 0.8482701

00:43:27.800 --> 00:43:30.292 We can just as easily express these

NOTE Confidence: 0.8482701

00:43:30.292 --> 00:43:32.359 indicators selectively in Gabaergic cells,

NOTE Confidence: 0.8482701

00:43:32.360 --> 00:43:34.260 in subtypes of Gabaergic cells,

NOTE Confidence: 0.8482701

00:43:34.260 --> 00:43:36.624 and derive these kinds of metrics

NOTE Confidence: 0.8482701

00:43:36.624 --> 00:43:37.806 for all different.

NOTE Confidence: 0.8482701

00:43:37.810 --> 00:43:39.808 Cortical neurons to learn about how

NOTE Confidence: 0.8482701

00:43:39.808 --> 00:43:41.760 different cell types are connected.

NOTE Confidence: 0.8482701

00:43:41.760 --> 00:43:44.624 We can almost go one better than that.

NOTE Confidence: 0.8482701

00:43:44.630 --> 00:43:47.094 What if it turns out that you have

NOTE Confidence: 0.8482701

00:43:47.094 --> 00:43:49.896 a mosaic animal in which some of its

NOTE Confidence: 0.8482701

00:43:49.896 --> 00:43:52.170 neurons are mutant or transgenic?

NOTE Confidence: 0.8482701

00:43:52.170 --> 00:43:53.960 Especially for maybe some interesting

NOTE Confidence: 0.8482701

00:43:53.960 --> 00:43:54.676 disease gene.

NOTE Confidence: 0.8482701

00:43:54.680 --> 00:43:57.011 We can then compare mutant cells and

NOTE Confidence: 0.8482701

00:43:57.011 --> 00:43:59.434 say wild type control cells from the

NOTE Confidence: 0.8482701

00:43:59.434 --> 00:44:01.941 same animal and ask how does the

NOTE Confidence: 0.8482701

00:44:01.941 --> 00:44:04.734 cell autonomous deletion of that gene alter?

NOTE Confidence: 0.8482701

00:44:04.740 --> 00:44:06.590 Or perhaps deletion of that

NOTE Confidence: 0.8482701

00:44:06.590 --> 00:44:08.070 gene cell autonomously disrupt?

NOTE Confidence: 0.8482701

00:44:08.070 --> 00:44:09.645 The large scale connectivity of

NOTE Confidence: 0.8482701

00:44:09.645 --> 00:44:10.275 those neurons.

NOTE Confidence: 0.8482701

00:44:10.280 --> 00:44:12.698 So essentially this gives us a

NOTE Confidence: 0.8482701

00:44:12.698 --> 00:44:14.852 very powerful readout into the

NOTE Confidence: 0.8482701

00:44:14.852 --> 00:44:16.720 connectivity of single cells.

NOTE Confidence: 0.8482701

00:44:16.720 --> 00:44:17.318 And again,

NOTE Confidence: 0.8482701

00:44:17.318 --> 00:44:19.112 this is this has been described

NOTE Confidence: 0.8482701

00:44:19.112 --> 00:44:21.117 in a paper from last year.

NOTE Confidence: 0.8482701

00:44:21.120 --> 00:44:21.449 OK,

NOTE Confidence: 0.8482701

00:44:21.449 --> 00:44:24.081 so in the last part of the talk

NOTE Confidence: 0.8482701

00:44:24.081 --> 00:44:26.644 I'm going to shift to something

NOTE Confidence: 0.8482701

00:44:26.644 --> 00:44:28.794 that is perhaps maybe a

NOTE Confidence: 0.8345697

00:44:28.880 --> 00:44:31.650 little bit more interesting to

NOTE Confidence: 0.8345697

00:44:31.650 --> 00:44:34.484 this Community, which is which is.

NOTE Confidence: 0.8345697

00:44:34.484 --> 00:44:37.070 Our work is very preclinical work.

NOTE Confidence: 0.8345697

00:44:37.070 --> 00:44:39.160 Nevertheless into models of neuro

NOTE Confidence: 0.8345697

00:44:39.160 --> 00:44:41.250 psychiatric disorders and my lab

NOTE Confidence: 0.8345697

00:44:41.320 --> 00:44:43.315 in close collaboration with just

NOTE Confidence: 0.8345697

00:44:43.315 --> 00:44:45.310 Cardens lab primarily works on

NOTE Confidence: 0.8345697

00:44:45.380 --> 00:44:47.408 autism spectrum disorder models.

NOTE Confidence: 0.8345697

00:44:47.410 --> 00:44:49.780 I'll just say from my perspective

NOTE Confidence: 0.8345697

00:44:49.780 --> 00:44:52.988 I this the notion of what these

NOTE Confidence: 0.8345697

00:44:52.988 --> 00:44:54.536 genetic models represents.

NOTE Confidence: 0.8345697

00:44:54.540 --> 00:44:55.608 Is not clear.

NOTE Confidence: 0.8345697

00:44:55.608 --> 00:44:57.744 I generally don't think that a

NOTE Confidence: 0.8345697

00:44:57.744 --> 00:44:59.796 mouse can be autistic in in a

NOTE Confidence: 0.8345697

00:44:59.796 --> 00:45:02.083 way that is is meaningful, right?

NOTE Confidence: 0.8345697

00:45:02.083 --> 00:45:03.798 These are animals in which

NOTE Confidence: 0.8345697

00:45:03.798 --> 00:45:04.827 we've deleted genes.

NOTE Confidence: 0.8345697

00:45:04.830 --> 00:45:06.545 Those jeans have been linked

NOTE Confidence: 0.8345697

00:45:06.545 --> 00:45:07.917 to autism spectrum disorders,

NOTE Confidence: 0.8345697

00:45:07.920 --> 00:45:09.936 and so we hope that these model

NOTE Confidence: 0.8345697

00:45:09.936 --> 00:45:12.102 systems give us insight into how

00:45:12.102 --> 00:45:13.750 genes regulate brain activity,

00:45:13.750 --> 00:45:15.170 how that ultimately translates

00:45:15.170 --> 00:45:16.590 into the clinical phenotypes

00:45:16.590 --> 00:45:17.988 associated with this disorder

00:45:17.988 --> 00:45:19.578 with these disorders is actually,

00:45:19.580 --> 00:45:21.638 I think, a much harder question,

00:45:21.640 --> 00:45:23.400 and something that is very

00:45:23.400 --> 00:45:25.770 difficult to do in a rodent.

00:45:25.770 --> 00:45:28.056 So I just want to put that out there

00:45:28.056 --> 00:45:30.449 'cause I feel sort of strongly about that.

00:45:30.450 --> 00:45:30.984 In fact,

00:45:30.984 --> 00:45:32.853 I think it puts the preclinical study

00:45:32.853 --> 00:45:34.784 in actually in a better position to

00:45:34.784 --> 00:45:37.026 not try to claim any sort of face

00:45:37.026 --> 00:45:38.694 validity and simply say these are.

00:45:38.700 --> 00:45:40.812 These are mechanistic studies to understand

NOTE Confidence: 0.8345697

00:45:40.812 --> 00:45:43.060 links between genes and brain activity.

NOTE Confidence: 0.8345697

00:45:43.060 --> 00:45:43.424 OK,

NOTE Confidence: 0.8345697

00:45:43.424 --> 00:45:46.336 so I'm going to tell you about our

NOTE Confidence: 0.8345697

00:45:46.336 --> 00:45:49.158 work in a model of Rett syndrome,

NOTE Confidence: 0.8345697

00:45:49.160 --> 00:45:49.890 you know,

NOTE Confidence: 0.8345697

00:45:49.890 --> 00:45:52.445 with the caveat that I just said

NOTE Confidence: 0.8345697

00:45:52.445 --> 00:45:54.544 attached and specifically these are

NOTE Confidence: 0.8345697

00:45:54.544 --> 00:45:57.540 going to be mice with mutations in me.

NOTE Confidence: 0.8345697

00:45:57.540 --> 00:45:57.891 CP2,

NOTE Confidence: 0.8345697

00:45:57.891 --> 00:46:00.699 methyl CPG binding protein 2 which is the

NOTE Confidence: 0.8345697

00:46:00.699 --> 00:46:03.250 causal gene disrupted in Rett syndrome,

NOTE Confidence: 0.8345697

00:46:03.250 --> 00:46:05.917 and so as many you probably know,

NOTE Confidence: 0.8345697

00:46:05.920 --> 00:46:07.936 Rett syndrome in human patients goes

NOTE Confidence: 0.8345697

00:46:07.936 --> 00:46:09.816 with with cognitive impairment with

NOTE Confidence: 0.8345697

00:46:09.816 --> 00:46:11.247 intellectual disability seizures.

NOTE Confidence: 0.8345697

00:46:11.250 --> 00:46:13.220 This sort of very characteristic

NOTE Confidence: 0.8345697

00:46:13.220 --> 00:46:14.796 loss of learned skills.

NOTE Confidence: 0.8345697

00:46:14.800 --> 00:46:16.060 Early in life,

NOTE Confidence: 0.8345697

00:46:16.060 --> 00:46:18.580 language deficits and then some really

NOTE Confidence: 0.8345697

00:46:18.580 --> 00:46:20.114 interesting stereotype and movements

NOTE Confidence: 0.8345697

00:46:20.114 --> 00:46:23.139 that also go with with a taxi as well.

NOTE Confidence: 0.8345697

00:46:23.140 --> 00:46:24.112 For you know,

NOTE Confidence: 0.8345697

00:46:24.112 --> 00:46:26.859 just just for saying that me CP2 is

NOTE Confidence: 0.8345697

00:46:26.859 --> 00:46:29.307 a is a transcriptional regulator and

NOTE Confidence: 0.8345697

00:46:29.307 --> 00:46:31.781 so it's disruption causes an enormous

NOTE Confidence: 0.8345697

00:46:31.781 --> 00:46:34.127 host of changes at the genetic,

NOTE Confidence: 0.8345697

00:46:34.130 --> 00:46:35.698 molecular and cellular level.

NOTE Confidence: 0.8345697

00:46:35.698 --> 00:46:38.050 So really we're looking at that

NOTE Confidence: 0.8345697

00:46:38.115 --> 00:46:39.655 sort of functional consequences

NOTE Confidence: 0.8345697

00:46:39.655 --> 00:46:42.719 of disruption of a gene that has a

NOTE Confidence: 0.8345697

00:46:42.719 --> 00:46:45.113 number of pathways that can interact with.

NOTE Confidence: 0.78669685

00:46:47.360 --> 00:46:49.915 So the really cool thing that we've

NOTE Confidence: 0.78669685

00:46:49.915 --> 00:46:51.348 discovered works, maybe surprisingly,

NOTE Confidence: 0.78669685

00:46:51.348 --> 00:46:53.442 and so this is work that's

NOTE Confidence: 0.78669685

00:46:53.442 --> 00:46:55.390 been done by Antara Majumdar,

NOTE Confidence: 0.78669685

00:46:55.390 --> 00:46:58.460 who is a post grad in the card lab and

NOTE Confidence: 0.78669685

00:46:58.541 --> 00:47:01.445 repent who is a technician in the card

NOTE Confidence: 0.78669685

00:47:01.445 --> 00:47:04.518 lab is to take these viral vectors.

NOTE Confidence: 0.78669685

00:47:04.520 --> 00:47:06.160 And I previously showed you

NOTE Confidence: 0.78669685

00:47:06.160 --> 00:47:08.253 that they work really well for

NOTE Confidence: 0.78669685

00:47:08.253 --> 00:47:10.198 expressing G cap or cholinergic

NOTE Confidence: 0.78669685

00:47:10.198 --> 00:47:12.180 indicators everywhere in the brain.

NOTE Confidence: 0.78669685

00:47:12.180 --> 00:47:14.095 They also work really well

NOTE Confidence: 0.78669685

00:47:14.095 --> 00:47:16.010 for driving crisper cast 9.

NOTE Confidence: 0.78669685

00:47:16.010 --> 00:47:18.838 Related proteins and so for these mice,

NOTE Confidence: 0.78669685

00:47:18.840 --> 00:47:21.521 these are transgenic mice in which CAS

00:47:21.521 --> 00:47:24.488 9 is expressed in all excitatory cells,

00:47:24.490 --> 00:47:26.920 so these mice are otherwise fine.

00:47:26.920 --> 00:47:30.088 It just turns out at the moment it's

00:47:30.088 --> 00:47:31.760 methodologically easier to start

00:47:31.760 --> 00:47:33.785 with the transgenic kastein mouse,

00:47:33.790 --> 00:47:36.142 so these might express cast 9

00:47:36.142 --> 00:47:38.230 in all their excitatory cells.

00:47:38.230 --> 00:47:41.058 We then inject two different viral vectors.

00:47:41.060 --> 00:47:42.218 These AAV 9,

00:47:42.218 --> 00:47:44.534 one is driving a GFP tagged

00:47:44.534 --> 00:47:46.778 guide RNA targeting me CP2.

00:47:46.780 --> 00:47:48.558 And for some experiments I'll show you

00:47:48.558 --> 00:47:50.799 in a second another is just driving

00:47:50.799 --> 00:47:52.579 this red fluorescent calcium indicator.

00:47:52.580 --> 00:47:54.660 Our camp one be so first here in

00:47:54.660 --> 00:47:56.872 the center is just a little bit

NOTE Confidence: 0.78669685

00:47:56.872 --> 00:47:58.502 of confirmation that this crisper

NOTE Confidence: 0.78669685

00:47:58.569 --> 00:47:59.897 cast 9 strategy works.

NOTE Confidence: 0.78669685

00:47:59.900 --> 00:48:02.340 So what you see on the left panel?

NOTE Confidence: 0.78669685

00:48:02.340 --> 00:48:03.228 That's the guide.

NOTE Confidence: 0.78669685

00:48:03.228 --> 00:48:05.300 RNA and GFP expression that that again

NOTE Confidence: 0.78669685

00:48:05.353 --> 00:48:07.516 you see pretty much throughout the brain.

NOTE Confidence: 0.78669685

00:48:07.520 --> 00:48:09.676 And here on the right the red

NOTE Confidence: 0.78669685

00:48:09.676 --> 00:48:11.185 is staining for me, CP2,

NOTE Confidence: 0.78669685

00:48:11.185 --> 00:48:12.710 the green is the GFP.

NOTE Confidence: 0.78669685

00:48:12.710 --> 00:48:14.796 The guide RNA expressing cells and you'll

NOTE Confidence: 0.78669685

00:48:14.796 --> 00:48:16.977 see that there's really no overlap there.

NOTE Confidence: 0.78669685

00:48:16.980 --> 00:48:18.284 So basically every cell.

NOTE Confidence: 0.78669685

00:48:18.284 --> 00:48:19.588 It has guide RNA.

NOTE Confidence: 0.78669685

00:48:19.590 --> 00:48:21.600 We have successfully deleted me CP2

NOTE Confidence: 0.78669685

00:48:21.600 --> 00:48:23.260 expression and that's shown here.

NOTE Confidence: 0.78669685

00:48:23.260 --> 00:48:24.920 You know for the population,

NOTE Confidence: 0.78669685

00:48:24.920 --> 00:48:26.252 so control mice have.

NOTE Confidence: 0.78669685

00:48:26.252 --> 00:48:28.580 You know, roughly 90% expression of me.

NOTE Confidence: 0.78669685

00:48:28.580 --> 00:48:29.928 CP2 in all cells.

NOTE Confidence: 0.78669685

00:48:29.928 --> 00:48:32.250 And that's not down to about 20%

NOTE Confidence: 0.78669685

00:48:32.250 --> 00:48:34.574 expression in the in the crisper model.

NOTE Confidence: 0.78669685

00:48:34.580 --> 00:48:35.908 So it's not perfect,

NOTE Confidence: 0.78669685

00:48:35.908 --> 00:48:37.568 but I'll also point out,

NOTE Confidence: 0.78669685

00:48:37.570 --> 00:48:39.568 right that cast 9 is only

NOTE Confidence: 0.78669685

00:48:39.568 --> 00:48:40.900 in the excitatory cells,

NOTE Confidence: 0.78669685

00:48:40.900 --> 00:48:42.903 which is only about 80% of

NOTE Confidence: 0.78669685

00:48:42.903 --> 00:48:43.902 all cortical neurons.

NOTE Confidence: 0.78669685

00:48:43.902 --> 00:48:45.900 So since this is about 20%,

NOTE Confidence: 0.78669685

00:48:45.900 --> 00:48:48.609 it's actually suggestive that were in fact.

NOTE Confidence: 0.78669685

00:48:48.610 --> 00:48:50.570 Probably deleting me CP2 from

NOTE Confidence: 0.78669685

00:48:50.570 --> 00:48:52.530 almost all the excitatory cells

NOTE Confidence: 0.78669685

00:48:52.599 --> 00:48:54.399 that are expressing kastein.

NOTE Confidence: 0.78669685

00:48:54.400 --> 00:48:56.444 You could do this in a transgenic

NOTE Confidence: 0.78669685

00:48:56.444 --> 00:48:58.196 mouse in which kastein was

NOTE Confidence: 0.78669685

00:48:58.196 --> 00:48:59.820 even more broadly expressed,

NOTE Confidence: 0.78669685

00:48:59.820 --> 00:49:01.520 and we would presumably have

NOTE Confidence: 0.78669685

00:49:01.520 --> 00:49:02.880 even even larger effects,

NOTE Confidence: 0.78669685

00:49:02.880 --> 00:49:05.512 and then this is just a Western blot

NOTE Confidence: 0.78669685

00:49:05.512 --> 00:49:07.853 data showing as a function of me

NOTE Confidence: 0.78669685

00:49:07.853 --> 00:49:09.896 CP2 protein and controls the crisper

NOTE Confidence: 0.78669685

00:49:09.896 --> 00:49:12.704 mutants show about a 75% reduction in MCP,

NOTE Confidence: 0.78669685

00:49:12.704 --> 00:49:13.380 two protein,

NOTE Confidence: 0.78669685

00:49:13.380 --> 00:49:15.802 and this is in comparison to a

NOTE Confidence: 0.78669685

00:49:15.802 --> 00:49:17.431 standard knockout for me, CP2,

NOTE Confidence: 0.78669685

00:49:17.431 --> 00:49:19.036 which shows an almost complete

NOTE Confidence: 0.78669685

00:49:19.036 --> 00:49:21.180 loss of of me CP2 protein.

NOTE Confidence: 0.78669685

00:49:21.180 --> 00:49:22.125 So somewhat remarkably,

NOTE Confidence: 0.78669685

00:49:22.125 --> 00:49:24.970 you can use viral vectors in an otherwise.

NOTE Confidence: 0.78669685

00:49:24.970 --> 00:49:26.878 Wild type mouse and get robust

NOTE Confidence: 0.78669685

00:49:26.878 --> 00:49:28.520 loss of me CP two.

NOTE Confidence: 0.78669685

00:49:28.520 --> 00:49:30.900 So does that mean anything

NOTE Confidence: 0.78669685

00:49:30.900 --> 00:49:32.804 functionally for these animals?

NOTE Confidence: 0.78669685

00:49:32.810 --> 00:49:34.964 So now this is work analytical

NOTE Confidence: 0.78669685

00:49:34.964 --> 00:49:37.159 work done by Hospice Tia postdoc

NOTE Confidence: 0.78669685

00:49:37.159 --> 00:49:39.217 in my lab and lavonna Mark,

NOTE Confidence: 0.78669685

00:49:39.220 --> 00:49:41.578 who is a Yale Singapore undergraduate

NOTE Confidence: 0.78669685

00:49:41.578 --> 00:49:44.123 who's been Co advised by Jess and

NOTE Confidence: 0.78669685

00:49:44.123 --> 00:49:46.223 I an lavonna was just admitted to

NOTE Confidence: 0.76190263

00:49:46.292 --> 00:49:47.760 the Yellae NP program.

NOTE Confidence: 0.76190263

00:49:47.760 --> 00:49:49.910 It's we're aggressively trying to

NOTE Confidence: 0.76190263

00:49:49.910 --> 00:49:52.679 convince her that she wants to to

NOTE Confidence: 0.76190263

00:49:52.679 --> 00:49:54.871 come to Yale for her PhD as well.

NOTE Confidence: 0.76190263

00:49:54.880 --> 00:49:57.706 So what had Austin lab did was the same

NOTE Confidence: 0.76190263

00:49:57.706 --> 00:50:00.399 kinds of correlational analysis that I?

NOTE Confidence: 0.76190263

00:50:00.400 --> 00:50:02.472 And you about so these are these

NOTE Confidence: 0.76190263

00:50:02.472 --> 00:50:04.324 are just matrices showing the

NOTE Confidence: 0.76190263

00:50:04.324 --> 00:50:06.124 pairwise correlations of activity

NOTE Confidence: 0.76190263

00:50:06.124 --> 00:50:07.924 in different cortical regions.

NOTE Confidence: 0.76190263

00:50:07.930 --> 00:50:10.012 And they're going to use graph

NOTE Confidence: 0.76190263

00:50:10.012 --> 00:50:11.686 theory based analysis, and again,

NOTE Confidence: 0.76190263

00:50:11.686 --> 00:50:14.190 I'm going to kind of just just blow

NOTE Confidence: 0.76190263

00:50:14.267 --> 00:50:16.605 through any of the details here and

NOTE Confidence: 0.76190263

00:50:16.605 --> 00:50:19.207 tell you that the variable I'm going

NOTE Confidence: 0.76190263

00:50:19.207 --> 00:50:21.499 to show you is called centrality.

NOTE Confidence: 0.76190263

00:50:21.500 --> 00:50:23.185 And it's really a mathematical

NOTE Confidence: 0.76190263

00:50:23.185 --> 00:50:25.330 representation of how a given parcel.

NOTE Confidence: 0.76190263

00:50:25.330 --> 00:50:27.766 In this case they have blue dots,

NOTE Confidence: 0.76190263

00:50:27.770 --> 00:50:30.546 is connected with the rest of the cortex,

NOTE Confidence: 0.76190263

00:50:30.550 --> 00:50:33.394 so a a blue dot that is directly or

NOTE Confidence: 0.76190263

00:50:33.394 --> 00:50:35.964 indirectly coupled to a small number of

NOTE Confidence: 0.76190263

00:50:35.964 --> 00:50:38.659 other regions would have a low centrality.

NOTE Confidence: 0.76190263

00:50:38.660 --> 00:50:40.683 Whereas a region of blue dot that's

NOTE Confidence: 0.76190263

00:50:40.683 --> 00:50:43.085 really connected to a whole lot of other

NOTE Confidence: 0.76190263

00:50:43.085 --> 00:50:44.560 regions would have high centrality.

NOTE Confidence: 0.76190263

00:50:44.560 --> 00:50:47.465 So it's it's just a measure of

NOTE Confidence: 0.76190263

00:50:47.465 --> 00:50:49.149 how functionally connected one

NOTE Confidence: 0.76190263

00:50:49.149 --> 00:50:50.969 area is with with another.

NOTE Confidence: 0.76190263

00:50:50.970 --> 00:50:52.740 So the first thing I'm going

NOTE Confidence: 0.76190263

00:50:52.740 --> 00:50:54.340 to show you is this,

NOTE Confidence: 0.76190263

00:50:54.340 --> 00:50:55.560 which is probably very

NOTE Confidence: 0.76190263

00:50:55.560 --> 00:50:57.085 difficult to make sense of,

NOTE Confidence: 0.76190263

00:50:57.090 --> 00:50:58.980 but I throw up here just really

NOTE Confidence: 0.76190263

00:50:58.980 --> 00:51:00.424 quickly and what we've plotted

NOTE Confidence: 0.76190263

00:51:00.424 --> 00:51:02.146 here now is the centrality for

NOTE Confidence: 0.76190263

00:51:02.146 --> 00:51:04.128 all of these different regions.

NOTE Confidence: 0.76190263

00:51:04.130 --> 00:51:04.434 Again,

NOTE Confidence: 0.76190263

00:51:04.434 --> 00:51:05.954 all the different cortical regions

NOTE Confidence: 0.76190263

00:51:05.954 --> 00:51:07.490 comparing control mice in black,

NOTE Confidence: 0.76190263

00:51:07.490 --> 00:51:09.639 the black bars and the ME CP2.

NOTE Confidence: 0.76190263

00:51:09.640 --> 00:51:10.684 CRISPR mutants in Gray.

NOTE Confidence: 0.76190263

00:51:10.684 --> 00:51:12.250 And then we divide that up

NOTE Confidence: 0.76190263

00:51:12.302 --> 00:51:13.918 into quiescence and locomotion.

NOTE Confidence: 0.76190263

00:51:13.920 --> 00:51:16.062 And so you can sort of squinted

NOTE Confidence: 0.76190263

00:51:16.062 --> 00:51:16.980 this from bed,

NOTE Confidence: 0.76190263

00:51:16.980 --> 00:51:18.750 and you'll see that there are

NOTE Confidence: 0.76190263

00:51:18.750 --> 00:51:20.323 some differences in the bars

NOTE Confidence: 0.76190263

00:51:20.323 --> 00:51:21.659 in different regions and.

NOTE Confidence: 0.76190263

00:51:21.660 --> 00:51:25.520 If you want us to let your eyes go to that,

NOTE Confidence: 0.76190263

00:51:25.520 --> 00:51:26.152 that's fine,

NOTE Confidence: 0.76190263

00:51:26.152 --> 00:51:29.138 but this is a little bit of an easier

NOTE Confidence: 0.76190263

00:51:29.138 --> 00:51:31.833 way to appreciate what we see here,

NOTE Confidence: 0.76190263

00:51:31.840 --> 00:51:33.595 and it's similar for quiescence

NOTE Confidence: 0.76190263

00:51:33.595 --> 00:51:34.297 in locomotion.

NOTE Confidence: 0.76190263

00:51:34.300 --> 00:51:36.400 So I'll just describe quiescence here.

NOTE Confidence: 0.76190263

00:51:36.400 --> 00:51:38.155 What I'm plotting here is

NOTE Confidence: 0.76190263

00:51:38.155 --> 00:51:39.559 the difference in centrality.

NOTE Confidence: 0.76190263

00:51:39.560 --> 00:51:39.873 Basically,

NOTE Confidence: 0.76190263

00:51:39.873 --> 00:51:42.377 the black bars minus the Gray bars up

NOTE Confidence: 0.76190263

00:51:42.377 --> 00:51:44.828 here for each different cortical region,

NOTE Confidence: 0.76190263

00:51:44.830 --> 00:51:46.936 so it's the it's the controls

NOTE Confidence: 0.76190263

00:51:46.936 --> 00:51:47.989 minus the mutants,

NOTE Confidence: 0.76190263

00:51:47.990 --> 00:51:49.740 so everywhere that it's red,

NOTE Confidence: 0.76190263

00:51:49.740 --> 00:51:51.670 it means the controls are.

NOTE Confidence: 0.76190263

00:51:51.670 --> 00:51:54.400 More connected and everywhere that it's blue,

NOTE Confidence: 0.76190263

00:51:54.400 --> 00:51:57.018 it means that the mutants show higher

NOTE Confidence: 0.76190263

00:51:57.018 --> 00:51:59.809 connectivity and so you can see this

NOTE Confidence: 0.76190263

00:51:59.809 --> 00:52:01.413 is very spatially heterogeneous.

NOTE Confidence: 0.76190263

00:52:01.420 --> 00:52:03.100 There's some really interesting

NOTE Confidence: 0.76190263

00:52:03.100 --> 00:52:05.200 networks whereby in some cases

NOTE Confidence: 0.76190263

00:52:05.200 --> 00:52:06.742 mutants show higher connectivity

NOTE Confidence: 0.76190263

00:52:06.742 --> 00:52:09.220 and in others the the controls do,

NOTE Confidence: 0.76190263

00:52:09.220 --> 00:52:11.068 and that's roughly similar,

NOTE Confidence: 0.76190263

00:52:11.068 --> 00:52:12.916 although not perfectly similar

NOTE Confidence: 0.76190263

00:52:12.916 --> 00:52:15.678 as a function of brain state.

NOTE Confidence: 0.76190263

00:52:15.680 --> 00:52:18.208 So this is really where I said at

NOTE Confidence: 0.76190263

00:52:18.208 --> 00:52:20.395 the very beginning that some of

NOTE Confidence: 0.76190263

00:52:20.395 --> 00:52:23.118 the data we're going to be quite

NOTE Confidence: 0.76190263

00:52:23.118 --> 00:52:26.149 preliminary and this is these are these.

NOTE Confidence: 0.76190263

00:52:26.150 --> 00:52:26.898 Are they?

NOTE Confidence: 0.76190263

00:52:26.898 --> 00:52:29.890 So I don't fully know what this means,

NOTE Confidence: 0.76190263

00:52:29.890 --> 00:52:32.172 but what it's telling us is that

NOTE Confidence: 0.76190263

00:52:32.172 --> 00:52:34.033 these this mutation strategy allows

NOTE Confidence: 0.76190263

00:52:34.033 --> 00:52:36.481 us to see very different patterns

NOTE Confidence: 0.76190263

00:52:36.481 --> 00:52:38.488 of connectivity across the cortex,

NOTE Confidence: 0.76190263

00:52:38.490 --> 00:52:40.435 suggesting that these might be

NOTE Confidence: 0.76190263

00:52:40.435 --> 00:52:42.979 classical disruptions seen in some of these.

NOTE Confidence: 0.83340013

00:52:42.980 --> 00:52:44.995 Some of these models of

NOTE Confidence: 0.83340013

00:52:44.995 --> 00:52:46.204 autism spectrum disorder.

NOTE Confidence: 0.83340013

00:52:46.210 --> 00:52:48.408 I'm not going to see any data,

NOTE Confidence: 0.83340013

00:52:48.410 --> 00:52:50.802 but I will say that we have worked

NOTE Confidence: 0.83340013

00:52:50.802 --> 00:52:52.798 on another gene called REI One,

NOTE Confidence: 0.83340013

00:52:52.800 --> 00:52:54.588 which is retinoic acid induced gene

NOTE Confidence: 0.83340013

00:52:54.588 --> 00:52:57.220 one which is the causal gene and Smith

NOTE Confidence: 0.83340013

00:52:57.220 --> 00:52:59.284 Magenis syndrome and it actually looks

NOTE Confidence: 0.83340013

00:52:59.348 --> 00:53:01.644 quite similar and an REI wanted me to

NOTE Confidence: 0.83340013

00:53:01.644 --> 00:53:03.790 have nothing to do with each other,

NOTE Confidence: 0.83340013

00:53:03.790 --> 00:53:05.300 so it's really quite intriguing

NOTE Confidence: 0.83340013

00:53:05.300 --> 00:53:07.148 and what we've sort of started

NOTE Confidence: 0.83340013

00:53:07.148 --> 00:53:09.340 this project to look at is to ask

NOTE Confidence: 0.83340013

00:53:09.340 --> 00:53:11.443 whether or not different models of

NOTE Confidence: 0.83340013

00:53:11.443 --> 00:53:12.855 autism spectrum disorders which

NOTE Confidence: 0.83340013

00:53:12.855 --> 00:53:14.152 made genetically or molecularly

NOTE Confidence: 0.83340013

00:53:14.152 --> 00:53:16.350 have nothing to do with each other,

NOTE Confidence: 0.83340013

00:53:16.350 --> 00:53:18.378 converge on similar network level phenotypes.

NOTE Confidence: 0.83340013

00:53:18.380 --> 00:53:20.076 And so this is sort of an example

NOTE Confidence: 0.83340013

00:53:20.076 --> 00:53:22.103 of the kinds of network phenotypes

NOTE Confidence: 0.83340013

00:53:22.103 --> 00:53:23.643 that we're actively exploring,

NOTE Confidence: 0.83340013

00:53:23.650 --> 00:53:26.116 and in some of these models.

NOTE Confidence: 0.83340013

00:53:26.120 --> 00:53:28.184 And you might imagine could easily

NOTE Confidence: 0.83340013

00:53:28.184 --> 00:53:30.368 be applied to whatever your favorite

NOTE Confidence: 0.83340013

00:53:30.368 --> 00:53:32.238 model of of neuro psychiatric

NOTE Confidence: 0.83340013

00:53:32.238 --> 00:53:34.603 disorders might be to the last slide

NOTE Confidence: 0.83340013

00:53:34.603 --> 00:53:36.373 that I'll show you is something

NOTE Confidence: 0.83340013

00:53:36.380 --> 00:53:37.604 that's perhaps equally cool,

NOTE Confidence: 0.83340013

00:53:37.604 --> 00:53:40.989 which is that we can do sort of some standard

NOTE Confidence: 0.83340013

00:53:40.989 --> 00:53:43.215 benchtop behavioral assays in these mice,

NOTE Confidence: 0.83340013

00:53:43.220 --> 00:53:44.930 and so in this case,

NOTE Confidence: 0.83340013

00:53:44.930 --> 00:53:47.317 this is the three Chamber sociability assay.

NOTE Confidence: 0.83340013

00:53:47.320 --> 00:53:49.330 You're simply asking whether or not

NOTE Confidence: 0.83340013

00:53:49.330 --> 00:53:51.421 a control or mutant mouse prefers

NOTE Confidence: 0.83340013

00:53:51.421 --> 00:53:53.479 to hang out with a conspecific,

NOTE Confidence: 0.83340013

00:53:53.480 --> 00:53:57.080 or prefers to hang out by itself in an empty.

NOTE Confidence: 0.83340013

00:53:57.080 --> 00:53:59.015 Cage and you'll see the

NOTE Confidence: 0.83340013

00:53:59.015 --> 00:54:00.563 control data shown here.

NOTE Confidence: 0.83340013

00:54:00.570 --> 00:54:02.901 This is sort of typical and I'll

NOTE Confidence: 0.83340013

104

00:54:02.901 --> 00:54:05.596 sort of be transparent and say this

NOTE Confidence: 0.83340013

00:54:05.596 --> 00:54:08.508 is the black bars are males and

NOTE Confidence: 0.83340013

00:54:08.508 --> 00:54:10.974 females lumped together that we don't

NOTE Confidence: 0.83340013

00:54:10.974 --> 00:54:13.371 see much of a difference between

NOTE Confidence: 0.83340013

00:54:13.371 --> 00:54:15.693 males and females of control mice.

NOTE Confidence: 0.83340013

00:54:15.700 --> 00:54:16.054 However,

NOTE Confidence: 0.83340013

00:54:16.054 --> 00:54:18.886 when we then look at the mutants and

NOTE Confidence: 0.83340013

00:54:18.886 --> 00:54:21.908 we divide them into males and females,

NOTE Confidence: 0.83340013

00:54:21.910 --> 00:54:24.238 we get very interesting and different

NOTE Confidence: 0.83340013

00:54:24.238 --> 00:54:25.794 phenotypes, whereas the males,

NOTE Confidence: 0.83340013

00:54:25.794 --> 00:54:28.133 the male mutants, much prefer to.

NOTE Confidence: 0.83340013

00:54:28.133 --> 00:54:29.306 To be alone,

NOTE Confidence: 0.83340013

00:54:29.310 --> 00:54:31.350 the female mutants show and even

NOTE Confidence: 0.83340013

00:54:31.350 --> 00:54:32.710 heightened preference for being

NOTE Confidence: 0.83340013

00:54:32.764 --> 00:54:33.720 with conspecifics,

NOTE Confidence: 0.83340013

00:54:33.720 --> 00:54:35.916 and so this is also preliminary.

NOTE Confidence: 0.83340013

00:54:35.920 --> 00:54:37.484 It's actually already significant,

NOTE Confidence: 0.83340013

00:54:37.484 --> 00:54:40.200 but this is sort of part of

NOTE Confidence: 0.83340013

00:54:40.200 --> 00:54:41.416 a much larger study,

NOTE Confidence: 0.83340013

00:54:41.420 --> 00:54:43.616 but I will sort of emphasize

NOTE Confidence: 0.83340013

00:54:43.616 --> 00:54:45.829 that these are these AAV mice.

NOTE Confidence: 0.83340013

00:54:45.830 --> 00:54:47.624 These were otherwise wild type C57

NOTE Confidence: 0.83340013

00:54:47.624 --> 00:54:49.782 mice that we used viral vectors to

NOTE Confidence: 0.83340013

00:54:49.782 --> 00:54:51.875 drive loss of functioning me CP two

NOTE Confidence: 0.83340013

00:54:51.940 --> 00:54:54.390 that produces both substantial network

NOTE Confidence: 0.83340013

00:54:54.390 --> 00:54:56.350 dysregulation and standard behavioral

NOTE Confidence: 0.83340013

00:54:56.350 --> 00:54:58.364 deficits seen in these mutants.

NOTE Confidence: 0.83340013

00:54:58.364 --> 00:55:00.269 So I think it illustrates.

NOTE Confidence: 0.83340013

00:55:00.270 --> 00:55:02.610 Through the power of these viral

NOTE Confidence: 0.83340013

00:55:02.610 --> 00:55:05.027 tools for expanding the OR for

NOTE Confidence: 0.83340013

00:55:05.027 --> 00:55:06.197 making more flexibel,

NOTE Confidence: 0.83340013

00:55:06.200 --> 00:55:07.780 the ability to study

NOTE Confidence: 0.83340013

00:55:07.780 --> 00:55:09.360 mutations of various genes.

NOTE Confidence: 0.845708

00:55:11.660 --> 00:55:14.024 So OK, so to summarize everything

NOTE Confidence: 0.845708

00:55:14.024 --> 00:55:15.980 that I've I've told you,

NOTE Confidence: 0.845708

00:55:15.980 --> 00:55:18.434 so one behavioral state is something

NOTE Confidence: 0.845708

00:55:18.434 --> 00:55:21.490 that we don't have a great handle on.

NOTE Confidence: 0.845708

00:55:21.490 --> 00:55:22.906 We define it operationally,

NOTE Confidence: 0.845708

00:55:22.906 --> 00:55:25.030 but it clearly corresponds to a

NOTE Confidence: 0.845708

00:55:25.090 --> 00:55:27.220 very high dimensional combination of

NOTE Confidence: 0.845708

00:55:27.220 --> 00:55:29.350 both motor and autonomic activity.

NOTE Confidence: 0.845708

00:55:29.350 --> 00:55:31.480 Arousal seems to be associated with

NOTE Confidence: 0.845708

00:55:31.480 --> 00:55:33.343 increases in both cholinergic signaling

NOTE Confidence: 0.845708

00:55:33.343 --> 00:55:35.278 and just general cortical activity

NOTE Confidence: 0.845708

00:55:35.278 --> 00:55:37.600 decreases in local circuit correlations.

NOTE Confidence: 0.845708

00:55:37.600 --> 00:55:39.540 But really interesting dynamic

NOTE Confidence: 0.845708

00:55:39.540 --> 00:55:41.965 changes in large scale correlations.

00:55:41.970 --> 00:55:44.602 Loss of me CP2 expression via this

00:55:44.602 --> 00:55:46.610 viral crisper strategy drives changes

00:55:46.610 --> 00:55:49.028 in both network activity as well

00:55:49.028 --> 00:55:51.046 as behavioral deficits and really

00:55:51.046 --> 00:55:53.332 sort of bring all that together.

00:55:53.340 --> 00:55:54.124 You know,

00:55:54.124 --> 00:55:56.868 simply to say that these viral vectors,

00:55:56.870 --> 00:55:58.046 music, scopic, imaging,

00:55:58.046 --> 00:55:58.830 genetic editing,

00:55:58.830 --> 00:56:00.600 all these strategies in combination

00:56:00.600 --> 00:56:02.370 provide incredibly powerful tools for

00:56:02.419 --> 00:56:04.307 dissecting relationships between cells,

00:56:04.310 --> 00:56:05.453 circuits, and behavior,

00:56:05.453 --> 00:56:08.679 and so let me just finish by acknowledging

00:56:08.679 --> 00:56:12.018 again everybody that did all the work.

00:56:12.020 --> 00:56:13.982 So Dan Barson did all of

NOTE Confidence: 0.845708

00:56:13.982 --> 00:56:16.000 the dual to Pizzo imaging.

NOTE Confidence: 0.845708

00:56:16.000 --> 00:56:17.158 Had Aspen, Insteon,

NOTE Confidence: 0.845708

00:56:17.158 --> 00:56:17.544 lavonna.

NOTE Confidence: 0.845708

00:56:17.544 --> 00:56:19.860 Mark Levan is also advised by

NOTE Confidence: 0.845708

00:56:19.936 --> 00:56:21.068 the by Jess Card,

NOTE Confidence: 0.845708

00:56:21.070 --> 00:56:23.982 and have been doing all of the graph

NOTE Confidence: 0.845708

00:56:23.982 --> 00:56:26.139 based analysis on this topic data.

NOTE Confidence: 0.845708

00:56:26.140 --> 00:56:26.864 Andrew Moberly,

NOTE Confidence: 0.845708

00:56:26.864 --> 00:56:29.398 an sweater Lohani in the card lab,

NOTE Confidence: 0.845708

00:56:29.400 --> 00:56:31.801 did all of the dual calcium an

NOTE Confidence: 0.845708

00:56:31.801 --> 00:56:33.653 acetylcholine imaging and Antara Majumdar

NOTE Confidence: 0.845708

00:56:33.653 --> 00:56:35.909 an remote Panton justice lab did.

NOTE Confidence: 0.845708

00:56:35.910 --> 00:56:37.785 The initial virus injections and

NOTE Confidence: 0.845708

00:56:37.785 --> 00:56:40.428 did all of the Histology of the

NOTE Confidence: 0.845708

00:56:40.428 --> 00:56:42.168 Western blotting data for the.

NOTE Confidence: 0.845708

00:56:42.170 --> 00:56:43.458 For the Christmas stuff,

NOTE Confidence: 0.845708

00:56:43.458 --> 00:56:45.390 we've been really generously funded by

NOTE Confidence: 0.845708

00:56:45.445 --> 00:56:47.019 both the NIH, the Simons Foundation,

NOTE Confidence: 0.845708

00:56:47.019 --> 00:56:48.534 and the Smith McGinnis Engine

NOTE Confidence: 0.845708

00:56:48.534 --> 00:56:49.140 Research Foundation.

NOTE Confidence: 0.845708

00:56:49.140 --> 00:56:50.650 For some of this work,

NOTE Confidence: 0.845708

00:56:50.650 --> 00:56:52.480 as well as getting important support

NOTE Confidence: 0.845708

00:56:52.480 --> 00:56:53.990 from the Copley Foundation here,

NOTE Confidence: 0.845708

00:56:53.990 --> 00:56:54.277 yeah,

NOTE Confidence: 0.845708

00:56:54.277 --> 00:56:56.286 so thank you all so much for

NOTE Confidence: 0.845708

00:56:56.286 --> 00:56:58.181 bearing with me and I'm happy

NOTE Confidence: 0.845708

00:56:58.181 --> 00:56:59.433 to answer any questions.

NOTE Confidence: 0.8789764

00:57:02.720 --> 00:57:04.519 Thank you Mike. Maybe you can stop

NOTE Confidence: 0.8789764

00:57:04.519 --> 00:57:06.333 sharing your screen and we can have

NOTE Confidence: 0.8789764

00:57:06.333 --> 00:57:07.573 people chime in with questions.

NOTE Confidence: 0.8789764

110

00:57:07.580 --> 00:57:09.632 There is 1. Technical question in

NOTE Confidence: 0.8789764

00:57:09.632 --> 00:57:12.112 the chat from Lauren Zima Low and

NOTE Confidence: 0.8789764

00:57:12.112 --> 00:57:14.200 the question was whether the controls

NOTE Confidence: 0.8789764

00:57:14.200 --> 00:57:16.407 5050 male and female or where they

NOTE Confidence: 0.8789764

00:57:16.407 --> 00:57:18.560 skewed in one way or the other.

NOTE Confidence: 0.8789764

00:57:18.560 --> 00:57:19.200 No, the

NOTE Confidence: 0.8051277

00:57:19.200 --> 00:57:21.108 yeah, so that's really quite preliminary.

NOTE Confidence: 0.8051277

00:57:21.110 --> 00:57:23.810 The controls there I I think it's I think

NOTE Confidence: 0.8051277

00:57:23.810 --> 00:57:26.124 those controls are six animals and I

NOTE Confidence: 0.8051277

00:57:26.124 --> 00:57:28.769 think it's two males and and for females.

NOTE Confidence: 0.8051277

00:57:28.770 --> 00:57:31.314 So in some sense you know you should.

NOTE Confidence: 0.8051277

00:57:31.320 --> 00:57:33.156 You should take those statistics as

NOTE Confidence: 0.8051277

00:57:33.156 --> 00:57:36.055 a with a bit of a grain of salt for

NOTE Confidence: 0.8051277

00:57:36.055 --> 00:57:38.020 sort of an internal presentation,

NOTE Confidence: 0.8051277

00:57:38.020 --> 00:57:40.006 but I would say though that.

NOTE Confidence: 0.8051277

00:57:40.010 --> 00:57:42.386 They're really for those six animals.

111

NOTE Confidence: 0.8051277

00:57:42.390 --> 00:57:44.760 The four females and two males.

NOTE Confidence: 0.8051277

00:57:44.760 --> 00:57:47.136 They're pretty similar in their distribution,

NOTE Confidence: 0.8051277

00:57:47.140 --> 00:57:50.695 and even if you just look at them separately,

NOTE Confidence: 0.8051277

00:57:50.700 --> 00:57:53.076 it's clear that the male and

NOTE Confidence: 0.8051277

00:57:53.076 --> 00:57:54.660 the female mutants really

NOTE Confidence: 0.8176789

00:57:54.660 --> 00:57:56.635 seemed to push well outside

NOTE Confidence: 0.8176789

00:57:56.635 --> 00:57:57.425 those distributions.

NOTE Confidence: 0.8176789

00:57:57.430 --> 00:57:59.410 So along those same lines,

NOTE Confidence: 0.8176789

00:57:59.410 --> 00:58:01.395 Huda Zoghbi's lab has extensively

NOTE Confidence: 0.8176789

00:58:01.395 --> 00:58:03.770 characterized the full knockouts of me.

NOTE Confidence: 0.8176789

00:58:03.770 --> 00:58:06.145 CP2 has she seen *** differences

NOTE Confidence: 0.8176789

00:58:06.145 --> 00:58:07.330 in social interaction?

NOTE Confidence: 0.8055031

00:58:09.640 --> 00:58:10.700 I don't believe so.

NOTE Confidence: 0.8055031

00:58:10.700 --> 00:58:13.229 I don't want to say no at all 'cause

NOTE Confidence: 0.8055031

00:58:13.229 --> 00:58:15.520 I don't know if she's ever shown it,

NOTE Confidence: 0.8055031

00:58:15.520 --> 00:58:16.942 but one of the I don't

NOTE Confidence: 0.8055031

00:58:16.942 --> 00:58:18.600 know if it's a weirdness,

NOTE Confidence: 0.8055031

00:58:18.600 --> 00:58:20.329 but it's one of the facts of

NOTE Confidence: 0.8055031

00:58:20.329 --> 00:58:22.239 the MCP 2 field in general.

NOTE Confidence: 0.8055031

00:58:22.240 --> 00:58:23.836 Is that most of the rodent

NOTE Confidence: 0.8055031

00:58:23.836 --> 00:58:25.600 work is done in the males.

NOTE Confidence: 0.8055031

00:58:25.600 --> 00:58:27.280 The males have much bigger phenotypes,

NOTE Confidence: 0.8055031

00:58:27.280 --> 00:58:29.472 so me Susan excellent gene and so most

NOTE Confidence: 0.8055031

00:58:29.472 --> 00:58:32.040 of the work has been done in the males,

NOTE Confidence: 0.8055031

00:58:32.040 --> 00:58:33.720 though as you probably are aware,

NOTE Confidence: 0.8055031

00:58:33.720 --> 00:58:35.750 in clinical cases it's much more often

NOTE Confidence: 0.8055031

00:58:35.750 --> 00:58:37.604 females that are considered now that

NOTE Confidence: 0.8055031

00:58:37.604 --> 00:58:39.464 maybe because even in the humans.

NOTE Confidence: 0.8055031

00:58:39.470 --> 00:58:42.414 Loss of any CP2 in males is so

NOTE Confidence: 0.8055031

00:58:42.414 --> 00:58:44.763 devastating that in many cases it

NOTE Confidence: 0.8055031

00:58:44.763 --> 00:58:47.061 may not be compatible with life.

00:58:47.070 --> 00:58:49.065 So that may be why the human

00:58:49.065 --> 00:58:51.127 studies are actually biased to the

00:58:51.127 --> 00:58:52.655 less severely affected subjects.

00:58:52.660 --> 00:58:55.612 So one of the nice parts about this also.

00:58:55.620 --> 00:58:58.102 OK, so first point as well, right?

00:58:58.102 --> 00:59:02.118 So our viral expression method is post Natal.

00:59:02.120 --> 00:59:02.668 You know,

00:59:02.668 --> 00:59:04.586 if you want to study prenatal changes,

00:59:04.590 --> 00:59:06.228 obviously that doesn't work for that.

00:59:06.230 --> 00:59:07.875 But if you want to say spare

00:59:07.875 --> 00:59:09.281 any really early disruption and

00:59:09.281 --> 00:59:10.886 look at gene function later,

00:59:10.890 --> 00:59:12.808 it has an advantage in that regard.

00:59:12.810 --> 00:59:15.025 So let's study some of these *** differences,

00:59:15.025 --> 00:59:16.855 perhaps a bit more easily than

00:59:16.855 --> 00:59:18.680 we might with the transgenics.

NOTE Confidence: 0.8055031

00:59:18.680 --> 00:59:18.950 Thank

NOTE Confidence: 0.78460616

00:59:18.950 --> 00:59:20.594 you, Zoran. Do you want to

NOTE Confidence: 0.78460616

00:59:20.594 --> 00:59:21.690 ask your other question?

NOTE Confidence: 0.79415023

00:59:24.500 --> 00:59:26.422 I'm not sure if I can be

NOTE Confidence: 0.79415023

00:59:26.422 --> 00:59:27.789 heard well and can click

NOTE Confidence: 0.79415023

00:59:27.790 --> 00:59:30.880 no logical challenges here so.

NOTE Confidence: 0.79415023

00:59:30.880 --> 00:59:34.288 Is it possible to Anna is really love this

NOTE Confidence: 0.79415023

00:59:34.288 --> 00:59:36.928 seminar and its high-end Tour de force

NOTE Confidence: 0.79415023

00:59:36.928 --> 00:59:39.658 fantastic in all these fluorescent tests?

NOTE Confidence: 0.79415023

00:59:39.660 --> 00:59:42.050 Sometimes in in a simpler models.

NOTE Confidence: 0.79415023

00:59:42.050 --> 00:59:44.446 It's good to put a some

NOTE Confidence: 0.79415023

00:59:44.446 --> 00:59:46.436 kind of a negative control.

NOTE Confidence: 0.79415023

00:59:46.440 --> 00:59:48.852 Would that be 2 technologically challenging

NOTE Confidence: 0.79415023

00:59:48.852 --> 00:59:51.229 or have you thought about that?

NOTE Confidence: 0.79415023

00:59:51.230 --> 00:59:54.022 Yeah, I don't like a third probe

NOTE Confidence: 0.79415023

00:59:54.022 --> 00:59:56.418 that doesn't react to anything yet.

NOTE Confidence: 0.79415023

00:59:56.418 --> 00:59:58.010 OK, said, that's a.

NOTE Confidence: 0.79415023

00:59:58.010 --> 01:00:00.026 That's a fantastic question.

NOTE Confidence: 0.79415023

01:00:00.026 --> 01:00:03.340 And so yeah, so I didn't go into

NOTE Confidence: 0.79415023

01:00:03.340 --> 01:00:06.220 a lot of the details, but so one.

NOTE Confidence: 0.79415023

01:00:06.220 --> 01:00:08.380 There's a lot to unpack there,

NOTE Confidence: 0.79415023

01:00:08.380 --> 01:00:11.308 so so yes, getting just sort of a

NOTE Confidence: 0.79415023

01:00:11.308 --> 01:00:13.600 basil readout of how much flora for

NOTE Confidence: 0.79415023

01:00:13.600 --> 01:00:16.376 is in in a given region is really

NOTE Confidence: 0.79415023

01:00:16.376 --> 01:00:18.812 sort of of critical and right,

NOTE Confidence: 0.79415023

01:00:18.820 --> 01:00:20.980 so you'd want some readout that

NOTE Confidence: 0.79415023

01:00:20.980 --> 01:00:22.060 wasn't activity dependent.

NOTE Confidence: 0.79415023

01:00:22.060 --> 01:00:24.220 More than that changes in hemodynamics,

NOTE Confidence: 0.79415023

01:00:24.220 --> 01:00:25.300 especially right because

NOTE Confidence: 0.79415023

01:00:25.300 --> 01:00:26.380 hemoglobin absorbs photons,

NOTE Confidence: 0.79415023

01:00:26.380 --> 01:00:28.540 especially in these visible light ranges,

NOTE Confidence: 0.79415023

01:00:28.540 --> 01:00:30.415 and that that absorption varies

NOTE Confidence: 0.79415023

01:00:30.415 --> 01:00:32.290 as a function of oxygenation.

NOTE Confidence: 0.79415023

01:00:32.290 --> 01:00:33.950 So there are hemodynamic artifacts

NOTE Confidence: 0.79415023

01:00:33.950 --> 01:00:36.569 in in a lot of this as well,

NOTE Confidence: 0.79415023

01:00:36.570 --> 01:00:38.275 so figuring out those controls

NOTE Confidence: 0.79415023

01:00:38.275 --> 01:00:40.840 is a huge part of what we do,

NOTE Confidence: 0.79415023

01:00:40.840 --> 01:00:42.628 and there are two ways that

NOTE Confidence: 0.79415023

01:00:42.628 --> 01:00:44.790 we do to get around that.

NOTE Confidence: 0.79415023

01:00:44.790 --> 01:00:47.414 So firstly, well, I didn't say this before.

NOTE Confidence: 0.79415023

01:00:47.420 --> 01:00:49.352 If you illuminate G camp with

NOTE Confidence: 0.79415023

01:00:49.352 --> 01:00:51.040 UV light instead of blue,

NOTE Confidence: 0.79415023

01:00:51.040 --> 01:00:52.364 it actually fluoresces independently

NOTE Confidence: 0.79415023

01:00:52.364 --> 01:00:54.019 of its calcium concentration and

NOTE Confidence: 0.79415023

01:00:54.019 --> 01:00:55.649 it basically behaves like GFP.

NOTE Confidence: 0.79415023

01:00:55.650 --> 01:00:57.462 So you can use UV illumination

NOTE Confidence: 0.79415023

01:00:57.462 --> 01:01:00.496 and the G camp as a as a sort

NOTE Confidence: 0.79415023

01:01:00.496 --> 01:01:01.900 of activity independent readout,

NOTE Confidence: 0.79415023

01:01:01.900 --> 01:01:04.628 and so that can be quite useful as

NOTE Confidence: 0.79415023

01:01:04.628 --> 01:01:08.658 a normalizing. Signal in addition.

NOTE Confidence: 0.79415023

01:01:08.660 --> 01:01:10.711 You can use fluctuations in that signal

NOTE Confidence: 0.79415023

01:01:10.711 --> 01:01:12.753 as a readout of hemodynamics because

NOTE Confidence: 0.79415023

01:01:12.753 --> 01:01:14.967 we know it's not calcium dependent,

NOTE Confidence: 0.79415023

01:01:14.970 --> 01:01:16.956 so any changes in that signal,

NOTE Confidence: 0.79415023

01:01:16.960 --> 01:01:18.268 or presumably from hemodynamics.

NOTE Confidence: 0.79415023

01:01:18.268 --> 01:01:20.230 We can also collect the backscattered

NOTE Confidence: 0.79415023

01:01:20.284 --> 01:01:20.940 green photons,

NOTE Confidence: 0.79415023

01:01:20.940 --> 01:01:23.005 so we're shining green light on that

NOTE Confidence: 0.79415023

01:01:23.005 --> 01:01:25.260 issue for the our camp fluorescence,

NOTE Confidence: 0.79415023

01:01:25.260 --> 01:01:27.916 so the our campus fluorescing in the red.

NOTE Confidence: 0.79415023

01:01:27.920 --> 01:01:29.966 But you can also measure the

NOTE Confidence: 0.79415023

118

01:01:29.966 --> 01:01:31.708 green photons that just bounce

NOTE Confidence: 0.79415023

01:01:31.708 --> 01:01:33.885 off the brain and come back up.

NOTE Confidence: 0.79415023

01:01:33.890 --> 01:01:35.550 Those are also very sensitive

NOTE Confidence: 0.79415023

01:01:35.550 --> 01:01:36.546 to hemodynamic changes,

NOTE Confidence: 0.79415023

01:01:36.550 --> 01:01:38.692 and so you can measure fluctuations in

NOTE Confidence: 0.79415023

01:01:38.692 --> 01:01:40.290 that backscattered green fluorescence.

NOTE Confidence: 0.79415023

01:01:40.290 --> 01:01:42.618 Is another readout for hemodynamics and

NOTE Confidence: 0.79415023

01:01:42.618 --> 01:01:44.545 then regress those hemodynamic signals

NOTE Confidence: 0.79415023

01:01:44.545 --> 01:01:46.722 out of the data to essentially correct

NOTE Confidence: 0.79415023

01:01:46.722 --> 01:01:48.789 for those those in accuracies does.

NOTE Confidence: 0.79415023

01:01:48.790 --> 01:01:52.300 That does that answer the question?

NOTE Confidence: 0.79415023

01:01:52.300 --> 01:01:53.638 Yes, it it.

NOTE Confidence: 0.79415023

01:01:53.638 --> 01:01:56.772 Even a ratio might be a possibility

NOTE Confidence: 0.79415023

01:01:56.772 --> 01:01:59.932 between those two and then you can

NOTE Confidence: 0.79415023

01:01:59.932 --> 01:02:02.130 actually standardize the output but.

NOTE Confidence: 0.84500885

01:02:04.150 --> 01:02:05.425 It must be too complicated

NOTE Confidence: 0.84500885

01:02:05.425 --> 01:02:07.430 to do in a real experiment.

NOTE Confidence: 0.84500885

01:02:07.430 --> 01:02:09.509 No, no. I mean, as I said,

NOTE Confidence: 0.84500885

01:02:09.510 --> 01:02:12.192 I mean we use a regression based approach to.

NOTE Confidence: 0.84500885

01:02:12.200 --> 01:02:14.540 I mean which is essentially a ratio, right?

NOTE Confidence: 0.84500885

01:02:14.540 --> 01:02:16.100 I mean the regression just gives

NOTE Confidence: 0.84500885

01:02:16.100 --> 01:02:17.984 you the beta coefficients for the

NOTE Confidence: 0.84500885

01:02:17.984 --> 01:02:19.384 basically the fractional contribution

NOTE Confidence: 0.84500885

01:02:19.384 --> 01:02:21.140 of 1 signal to the other.

NOTE Confidence: 0.84500885

01:02:21.140 --> 01:02:23.230 So thank you. Al

NOTE Confidence: 0.8994969

01:02:29.280 --> 01:02:33.278 I can't hear you. Aw, we can't hear you.

NOTE Confidence: 0.79152364

01:02:36.270 --> 01:02:39.564 Maybe put it in the chat and then

NOTE Confidence: 0.79152364

01:02:39.564 --> 01:02:42.860 and I'll answer. I'll ask it for you.

NOTE Confidence: 0.79152364

01:02:42.860 --> 01:02:46.568 OK, there you go OK is it working OK?

NOTE Confidence: 0.79152364

01:02:46.570 --> 01:02:47.809 Sorry bout that.

NOTE Confidence: 0.79152364

01:02:47.810 --> 01:02:51.509 So what I was wondering is a great talk.

NOTE Confidence: 0.79152364

01:02:51.510 --> 01:02:53.985 I was wondering about this discrepancy

NOTE Confidence: 0.79152364

01:02:53.985 --> 01:02:55.630 between decreased local correlations

NOTE Confidence: 0.79152364

01:02:55.630 --> 01:02:57.278 and increased global correlations

NOTE Confidence: 0.79152364

01:02:57.280 --> 01:02:59.340 during periods of high arousal.

NOTE Confidence: 0.79152364

01:02:59.340 --> 01:03:02.468 Yeah, and I was wondering if you steal

NOTE Confidence: 0.79152364

01:03:02.468 --> 01:03:06.278 that as relating to like the effects of.

NOTE Confidence: 0.79152364

01:03:06.280 --> 01:03:08.467 Is it a calling on Amex or this is

NOTE Confidence: 0.79152364

01:03:08.467 --> 01:03:11.160 sort of like spatial scales at which

NOTE Confidence: 0.79152364

01:03:11.160 --> 01:03:12.752 acetylcholine is being released?

NOTE Confidence: 0.79152364

01:03:12.760 --> 01:03:14.698 Like meaning maybe the the during

NOTE Confidence: 0.79152364

01:03:14.700 --> 01:03:16.850 high arousal it's be the fluctuations

NOTE Confidence: 0.79152364

01:03:16.850 --> 01:03:18.410 in acetylcholine are happening

NOTE Confidence: 0.79152364

01:03:18.410 --> 01:03:20.335 on more defined social spatial

NOTE Confidence: 0.79152364

01:03:20.335 --> 01:03:22.417 scale or or something like that?

NOTE Confidence: 0.79152364

01:03:22.420 --> 01:03:25.019 Yeah, I mean I think that's, uh,

NOTE Confidence: 0.79152364

01:03:25.019 --> 01:03:27.293 those are sort of the questions

NOTE Confidence: 0.79152364

01:03:27.293 --> 01:03:29.079 that we're asking as well,

NOTE Confidence: 0.79152364

01:03:29.080 --> 01:03:31.670 and I don't have any great answers,

NOTE Confidence: 0.79152364

01:03:31.670 --> 01:03:34.838 so it's been it's been shown recently by by

NOTE Confidence: 0.79152364

01:03:34.838 --> 01:03:38.330 a couple of labs that if you for example,

NOTE Confidence: 0.79152364

01:03:38.330 --> 01:03:39.449 I mean so.

NOTE Confidence: 0.79152364

01:03:39.449 --> 01:03:39.822 Firstly,

NOTE Confidence: 0.79152364

01:03:39.822 --> 01:03:41.314 individual basil forebrain neurons

NOTE Confidence: 0.79152364

01:03:41.314 --> 01:03:43.555 which are the main supplier of

NOTE Confidence: 0.79152364

01:03:43.555 --> 01:03:44.983 acetylcholine to the cortex,

NOTE Confidence: 0.79152364

01:03:44.990 --> 01:03:46.470 have pretty divergent axons.

NOTE Confidence: 0.79152364

01:03:46.470 --> 01:03:48.690 So some go to some places,

NOTE Confidence: 0.79152364

01:03:48.690 --> 01:03:49.970 some go to others,

NOTE Confidence: 0.79152364

01:03:49.970 --> 01:03:51.890 and so the coordination of acetylcholine

NOTE Confidence: 0.79152364

01:03:51.950 --> 01:03:53.710 release probably substantially involves

NOTE Confidence: 0.79152364

01:03:53.710 --> 01:03:56.350 the coordination or lack of coordination.

NOTE Confidence: 0.79152364

01:03:56.350 --> 01:03:57.814 Between individual neurons within

NOTE Confidence: 0.79152364

01:03:57.814 --> 01:04:00.347 the basal forebrain and so as we

NOTE Confidence: 0.79152364

01:04:00.347 --> 01:04:02.258 as we try to learn more about

NOTE Confidence: 0.79152364

01:04:02.258 --> 01:04:03.739 what regulates their activity,

NOTE Confidence: 0.79152364

01:04:03.740 --> 01:04:05.552 that's probably going to give us

NOTE Confidence: 0.79152364

01:04:05.552 --> 01:04:07.844 some insight into you know both the

NOTE Confidence: 0.79152364

01:04:07.844 --> 01:04:09.549 increases and then decreases the

NOTE Confidence: 0.79152364

01:04:09.549 --> 01:04:11.023 correlation of of acetylcholine

NOTE Confidence: 0.79152364

01:04:11.023 --> 01:04:12.479 release in the cortex.

NOTE Confidence: 0.79152364

01:04:12.480 --> 01:04:14.872 And there are also a small number of

NOTE Confidence: 0.79152364

01:04:14.872 --> 01:04:16.665 local interneurons within the cortex

NOTE Confidence: 0.79152364

01:04:16.665 --> 01:04:18.185 that can release acetylcholine.

NOTE Confidence: 0.79152364

01:04:18.190 --> 01:04:18.776 Quite honestly,

NOTE Confidence: 0.79152364

01:04:18.776 --> 01:04:20.827 I don't think we have an understanding

NOTE Confidence: 0.79152364

01:04:20.827 --> 01:04:22.558 of the relative contributions,

NOTE Confidence: 0.79152364

01:04:22.560 --> 01:04:22.892 right?

123

NOTE Confidence: 0.79152364

01:04:22.892 --> 01:04:23.556 Our assumption,

NOTE Confidence: 0.79152364

01:04:23.556 --> 01:04:25.548 although it's not based on a

NOTE Confidence: 0.79152364

01:04:25.548 --> 01:04:27.398 whole lot of quantitative data.

NOTE Confidence: 0.79152364

01:04:27.400 --> 01:04:29.182 Is that most of the acetylcholine

NOTE Confidence: 0.79152364

01:04:29.182 --> 01:04:30.823 that we're seeing comes from

NOTE Confidence: 0.79152364

01:04:30.823 --> 01:04:32.407 from basil forebrain projections?

NOTE Confidence: 0.79152364

01:04:32.410 --> 01:04:34.075 But but it's certainly possible

NOTE Confidence: 0.79152364

01:04:34.075 --> 01:04:35.074 that there's a.

NOTE Confidence: 0.79152364

01:04:35.080 --> 01:04:36.816 There's a substantial contribution

NOTE Confidence: 0.79152364

01:04:36.816 --> 01:04:39.830 from local release and that may play

NOTE Confidence: 0.79152364

01:04:39.830 --> 01:04:42.566 some role in whether you see you know

NOTE Confidence: 0.79152364

01:04:42.566 --> 01:04:44.619 increases or decreases correlation.

NOTE Confidence: 0.79152364

01:04:44.620 --> 01:04:47.760 Doctor data that was a great talk Mike.

NOTE Confidence: 0.79152364

01:04:47.760 --> 01:04:50.880 So just to follow up to ALS questions,

NOTE Confidence: 0.79152364

01:04:50.880 --> 01:04:53.160 I was wondering if it's possible

NOTE Confidence: 0.79152364

01:04:53.160 --> 01:04:55.602 that these local circuits are being

NOTE Confidence: 0.79152364

01:04:55.602 --> 01:04:57.589 entrained at a particular say,

NOTE Confidence: 0.79152364

01:04:57.590 --> 01:04:59.222 oscillatory frequency that permits

NOTE Confidence: 0.79152364

01:04:59.222 --> 01:05:00.854 greater coherence across these

NOTE Confidence: 0.79152364

01:05:00.854 --> 01:05:02.699 anatomically connected large scale circuits.

NOTE Confidence: 0.79152364

01:05:02.700 --> 01:05:05.840 Is that one sort of underlying sort of?

NOTE Confidence: 0.79152364

01:05:05.840 --> 01:05:07.810 Yeah, I mean very much,

NOTE Confidence: 0.79152364

01:05:07.810 --> 01:05:08.474 so right?

NOTE Confidence: 0.79152364

01:05:08.474 --> 01:05:10.798 I mean so gamma activity is certainly

NOTE Confidence: 0.79152364

01:05:10.798 --> 01:05:13.804 a proposed mechanism for a long time

NOTE Confidence: 0.79152364

01:05:13.804 --> 01:05:16.150 of coordinating long distance regions.

NOTE Confidence: 0.79152364

01:05:16.150 --> 01:05:19.166 One of the things that I didn't emphasize,

NOTE Confidence: 0.79152364

01:05:19.170 --> 01:05:21.426 mostly 'cause it's a problem that

NOTE Confidence: 0.79152364

01:05:21.426 --> 01:05:22.554 we can't fix,

NOTE Confidence: 0.79152364

01:05:22.560 --> 01:05:24.445 is that the calcium indicators

NOTE Confidence: 0.79152364

01:05:24.445 --> 01:05:25.576 are really slow,

NOTE Confidence: 0.79152364

01:05:25.580 --> 01:05:28.178 so the timescales over which we're

NOTE Confidence: 0.79152364

01:05:28.178 --> 01:05:29.910 seeing fluctuations are really

NOTE Confidence: 0.79152364

01:05:29.980 --> 01:05:31.975 slow on the order of you know,

NOTE Confidence: 0.79152364

01:05:31.980 --> 01:05:34.242 I could be generous and say

NOTE Confidence: 0.79152364

01:05:34.242 --> 01:05:35.373 hundreds of milliseconds,

NOTE Confidence: 0.79152364

01:05:35.380 --> 01:05:37.636 but probably even seconds you know,

NOTE Confidence: 0.79152364

01:05:37.640 --> 01:05:39.992 whereas you know gamma activity to

NOTE Confidence: 0.79152364

01:05:39.992 --> 01:05:41.983 to coordinate regions is obviously

NOTE Confidence: 0.79152364

01:05:41.983 --> 01:05:44.426 much faster than 40 Hertz or so,

NOTE Confidence: 0.79152364

01:05:44.430 --> 01:05:46.385 so it's possible that those

NOTE Confidence: 0.79152364

01:05:46.385 --> 01:05:47.558 oscillations could be.

NOTE Confidence: 0.79152364

01:05:47.560 --> 01:05:49.555 The envelope of those oscillations

NOTE Confidence: 0.79152364

01:05:49.555 --> 01:05:51.550 might be what we're seeing

NOTE Confidence: 0.8301324

01:05:51.623 --> 01:05:53.689 that you know, maybe the coordination

NOTE Confidence: 0.8301324

01:05:53.689 --> 01:05:56.370 is is driven by by gamma say,

NOTE Confidence: 0.8301324

01:05:56.370 --> 01:05:59.426 but that's all we really have access to.

NOTE Confidence: 0.8301324

01:05:59.430 --> 01:06:02.104 Might be the envelope of those correlations.

NOTE Confidence: 0.8301324

01:06:02.110 --> 01:06:03.910 It's really challenging with calcium

NOTE Confidence: 0.8301324

01:06:03.910 --> 01:06:06.710 imaging to get a more direct readout.

NOTE Confidence: 0.8301324

01:06:06.710 --> 01:06:08.650 We're optimistic, though we haven't

NOTE Confidence: 0.8301324

01:06:08.650 --> 01:06:10.920 really gotten it to work yet.

NOTE Confidence: 0.8301324

01:06:10.920 --> 01:06:12.069 That voltage imaging,

NOTE Confidence: 0.8301324

01:06:12.069 --> 01:06:14.367 especially with the music scale approach,

NOTE Confidence: 0.8301324

01:06:14.370 --> 01:06:16.764 may provide an ability to see

NOTE Confidence: 0.8301324

01:06:16.764 --> 01:06:18.360 fluctuations like like gamma

NOTE Confidence: 0.8301324

01:06:18.434 --> 01:06:20.498 at this sort of spatial scale,

NOTE Confidence: 0.8301324

01:06:20.500 --> 01:06:21.574 but that's that's.

NOTE Confidence: 0.8301324

01:06:21.574 --> 01:06:22.648 The bleeding edge.

NOTE Confidence: 0.8301324

01:06:22.650 --> 01:06:24.099 Sort of like just just past the

NOTE Confidence: 0.8301324

01:06:24.099 --> 01:06:25.668 bleeding edge at the moment and stuff.

NOTE Confidence: 0.78845793

01:06:28.790 --> 01:06:32.027 I just wanted to to make a note

NOTE Confidence: 0.78845793

01:06:32.027 --> 01:06:34.419 that using the same sensor,

NOTE Confidence: 0.78845793

01:06:34.420 --> 01:06:37.066 the Estel cooling sensor and vibra

NOTE Confidence: 0.78845793

01:06:37.066 --> 01:06:38.830 photometry of principle neurons

NOTE Confidence: 0.78845793

01:06:38.903 --> 01:06:40.908 in the basal lateral amygdala,

NOTE Confidence: 0.78845793

01:06:40.910 --> 01:06:43.640 we also see fairly clear dissociation

NOTE Confidence: 0.78845793

01:06:43.640 --> 01:06:46.329 between the activity of Astle colon

NOTE Confidence: 0.78845793

01:06:46.329 --> 01:06:49.094 and the structure of the release of

NOTE Confidence: 0.78845793

01:06:49.094 --> 01:06:51.735 Astle calling in the structure and

NOTE Confidence: 0.78845793

01:06:51.735 --> 01:06:54.333 coordination of firing of the entire

NOTE Confidence: 0.78845793

01:06:54.333 --> 01:06:56.498 excitatory network in the structure.

NOTE Confidence: 0.78845793

01:06:56.500 --> 01:06:58.670 So if it is inducing,

NOTE Confidence: 0.78845793

01:06:58.670 --> 01:07:01.328 let's say, local Theta, or like.

NOTE Confidence: 0.78845793

01:07:01.330 --> 01:07:03.385 Local gamma it's not sufficient

NOTE Confidence: 0.78845793

01:07:03.385 --> 01:07:05.440 to to coordinate the network.

NOTE Confidence: 0.78845793

01:07:05.440 --> 01:07:07.360 The excitatory network that doesn't

NOTE Confidence: 0.78845793

01:07:07.360 --> 01:07:09.794 mean that there isn't a selection

NOTE Confidence: 0.78845793

01:07:09.794 --> 01:07:12.019 of neurons within that network,

NOTE Confidence: 0.78845793

01:07:12.020 --> 01:07:15.429 but overall the rhythms are not sufficient

NOTE Confidence: 0.78845793

01:07:15.429 --> 01:07:18.758 to coordinate the whole network locally.

NOTE Confidence: 0.78845793

01:07:18.760 --> 01:07:19.981 So Doctor Cederbaum,

NOTE Confidence: 0.78845793

01:07:19.981 --> 01:07:22.860 you want to ask your question.

NOTE Confidence: 0.78845793

01:07:22.860 --> 01:07:26.690 Yeah, so I mean not to try to get out of

NOTE Confidence: 0.78845793

01:07:26.778 --> 01:07:29.496 the realm of what you've done too far.

NOTE Confidence: 0.78845793

01:07:29.500 --> 01:07:30.144 Risk getting.

NOTE Confidence: 0.78845793

01:07:30.144 --> 01:07:32.394 I don't know for an answer here,

NOTE Confidence: 0.78845793

01:07:32.394 --> 01:07:34.326 but wondering if there's an opportunity

NOTE Confidence: 0.85871965

01:07:34.330 --> 01:07:36.577 here. Also to study patterns of glial

NOTE Confidence: 0.85871965

01:07:36.577 --> 01:07:38.512 activity and whether there are receptors

NOTE Confidence: 0.85871965

01:07:38.512 --> 01:07:40.446 or channels that are specific to

NOTE Confidence: 0.85871965

01:07:40.446 --> 01:07:42.376 various glial populations that could be

NOTE Confidence: 0.85871965

01:07:42.376 --> 01:07:44.626 leveraged to do that with this technique?

NOTE Confidence: 0.85871965

01:07:44.630 --> 01:07:46.884 Yeah, it's funny. You should say that.

NOTE Confidence: 0.85871965

01:07:46.890 --> 01:07:49.581 So one of the things that I dearly dearly

NOTE Confidence: 0.85871965

01:07:49.581 --> 01:07:52.036 love about Yale and having been here,

NOTE Confidence: 0.85871965

01:07:52.040 --> 01:07:53.765 is how much amazing collaborations

NOTE Confidence: 0.85871965

01:07:53.765 --> 01:07:55.730 have sprung up here and so.

NOTE Confidence: 0.85871965

01:07:55.730 --> 01:07:57.000 So Carla Rothlin's answer of

NOTE Confidence: 0.85871965

01:07:57.000 --> 01:07:58.270 doshas groups have really been

NOTE Confidence: 0.85871965

01:07:58.319 --> 01:07:59.699 interested in neuroinflammation,

NOTE Confidence: 0.85871965

01:07:59.700 --> 01:08:00.916 particularly as regards astrocytes

NOTE Confidence: 0.85871965

01:08:00.916 --> 01:08:02.436 and glial cells in general.

NOTE Confidence: 0.85871965

01:08:02.440 --> 01:08:03.064 For awhile,

NOTE Confidence: 0.85871965

01:08:03.064 --> 01:08:05.248 and so we have a very nascent

NOTE Confidence: 0.85871965

01:08:05.248 --> 01:08:06.681 collaboration going on with them

NOTE Confidence: 0.85871965

01:08:06.681 --> 01:08:08.850 starting to look at at glial activity.

NOTE Confidence: 0.85871965

01:08:08.850 --> 01:08:11.226 So as I said, I mean all of these

NOTE Confidence: 0.85871965

01:08:11.226 --> 01:08:12.810 indicators are easily expressed,

NOTE Confidence: 0.85871965

01:08:12.810 --> 01:08:14.325 and I mean anything that

NOTE Confidence: 0.85871965

01:08:14.325 --> 01:08:16.170 you've got a pre line for.

NOTE Confidence: 0.85871965

01:08:16.170 --> 01:08:18.610 We can express it now that is a

NOTE Confidence: 0.85871965

01:08:18.610 --> 01:08:21.033 little bit of a rub right because

NOTE Confidence: 0.85871965

01:08:21.033 --> 01:08:23.343 it actually turns out and this is

NOTE Confidence: 0.85871965

01:08:23.343 --> 01:08:25.654 this is a bit new to me as well.

NOTE Confidence: 0.85871965

01:08:25.654 --> 01:08:26.990 Genetically targeting astrocytes is.

NOTE Confidence: 0.85871965

01:08:26.990 --> 01:08:29.906 Is not quite as easy as one might think,

NOTE Confidence: 0.85871965

01:08:29.910 --> 01:08:32.246 so it's been known for awhile that like

NOTE Confidence: 0.85871965

01:08:32.246 --> 01:08:34.764 GFP or at least the GFP cream mouse

NOTE Confidence: 0.85871965

01:08:34.764 --> 01:08:37.030 is not that specific for astrocytes.

NOTE Confidence: 0.85871965

01:08:37.030 --> 01:08:39.414 You do get neurons labeled and in fact

NOTE Confidence: 0.85871965

01:08:39.414 --> 01:08:42.122 even some of the more recent blinds that

NOTE Confidence: 0.85871965

01:08:42.122 --> 01:08:44.490 have been developed like like LDH Creek,

NOTE Confidence: 0.85871965

01:08:44.490 --> 01:08:45.654 may also label neurons,

NOTE Confidence: 0.85871965

01:08:45.654 --> 01:08:46.818 especially if if expressed

NOTE Confidence: 0.85871965

01:08:46.818 --> 01:08:48.050 early in development.

NOTE Confidence: 0.85871965

01:08:48.050 --> 01:08:50.318 So so yeah, we can do it.

NOTE Confidence: 0.85871965

01:08:50.320 --> 01:08:52.258 We're very interested in doing it,

NOTE Confidence: 0.85871965

01:08:52.260 --> 01:08:54.204 especially as a part of collaboration

NOTE Confidence: 0.85871965

01:08:54.204 --> 01:08:56.468 with some of the groups at Yale.

NOTE Confidence: 0.85871965

01:08:56.470 --> 01:08:57.862 There are some remaining

NOTE Confidence: 0.85871965

01:08:57.862 --> 01:08:58.558 methodological challenges.

NOTE Confidence: 0.85871965

01:08:58.560 --> 01:09:01.620 To making sure that the signals that we see

NOTE Confidence: 0.85871965

01:09:01.620 --> 01:09:04.707 say just come from the cells of interest,

NOTE Confidence: 0.85871965

01:09:04.710 --> 01:09:05.436 But yeah,

NOTE Confidence: 0.85871965

01:09:05.436 --> 01:09:05.799 yeah.

NOTE Confidence: 0.7894169

01:09:08.770 --> 01:09:10.876 Any other questions for Doctor Higley?

NOTE Confidence: 0.844044

01:09:13.820 --> 01:09:15.572 OK, well thank you all for

NOTE Confidence: 0.844044

01:09:15.572 --> 01:09:16.740 joining us this morning.

NOTE Confidence: 0.844044

01:09:16.740 --> 01:09:19.368 Thank you for taking time out of your day.

NOTE Confidence: 0.844044

01:09:19.370 --> 01:09:21.032 Thank you Mike for presenting these

NOTE Confidence: 0.844044

01:09:21.032 --> 01:09:22.445 interesting data and for pointing

NOTE Confidence: 0.844044

01:09:22.445 --> 01:09:23.993 out how the preclinical and the

NOTE Confidence: 0.844044

01:09:23.993 --> 01:09:25.790 clinical can be interpreted together.

NOTE Confidence: 0.844044

01:09:25.790 --> 01:09:28.418 I have 111 quick answer is I saw somebody

NOTE Confidence: 0.844044

01:09:28.420 --> 01:09:30.492 asked, does this map on to resting

NOTE Confidence: 0.844044

01:09:30.492 --> 01:09:32.750 state fMRI and so let me give one

NOTE Confidence: 0.844044

01:09:32.750 --> 01:09:34.736 other plug that was that you know

NOTE Confidence: 0.844044

01:09:34.736 --> 01:09:36.596 that's you one other plug right?

NOTE Confidence: 0.844044

01:09:36.600 --> 01:09:38.400 So so in a collaboration with

NOTE Confidence: 0.844044

01:09:38.400 --> 01:09:40.100 Todd Constables Lab here at Yale,

NOTE Confidence: 0.844044

01:09:40.100 --> 01:09:41.996 we also just published a paper.

NOTE Confidence: 0.844044

01:09:42.000 --> 01:09:43.890 In nature, methods doing simultaneous

NOTE Confidence: 0.844044

01:09:43.890 --> 01:09:45.402 miscopy calcium imaging and

NOTE Confidence: 0.844044

01:09:45.402 --> 01:09:47.077 fMRI and that's allowing us,

NOTE Confidence: 0.844044

01:09:47.080 --> 01:09:48.504 at least in mice,

NOTE Confidence: 0.844044

01:09:48.504 --> 01:09:49.928 to make direct relationships

NOTE Confidence: 0.844044

01:09:49.928 --> 01:09:51.439 pretty bold and calcium,

NOTE Confidence: 0.844044

01:09:51.440 --> 01:09:53.366 which we hope will at least

NOTE Confidence: 0.844044

01:09:53.366 --> 01:09:55.565 serve as a bridge for relating

NOTE Confidence: 0.844044

01:09:55.565 --> 01:09:57.670 the cellular level analysis to

NOTE Confidence: 0.844044

01:09:57.670 --> 01:09:59.788 human bold data as well so.

NOTE Confidence: 0.8478142

01:10:01.180 --> 01:10:03.700 Good way to good way to end.

NOTE Confidence: 0.8478142

01:10:03.700 --> 01:10:05.818 Excellent way to end. Thank you

NOTE Confidence: 0.8478142

01:10:05.818 --> 01:10:08.191 everybody and have a good weekend.