WEBVTT

NOTE duration: ”00:51:30.730”

NOTE Confidence: 0.86481214

00:00:00.160 --> 00:00:01.360 Joe gets his his time.

NOTE Confidence: 0.86481214

00:00:01.360 --> 00:00:02.420 So welcome everyone,

NOTE Confidence: 0.95919585

00:00:03.040 --> 00:00:04.240 to our February meeting of

NOTE Confidence: 0.95919585

00:00:04.240 --> 00:00:06.000 the, program for psychedelic science

NOTE Confidence: 0.95919585

00:00:06.000 --> 00:00:06.899 seminar series.

NOTE Confidence: 0.87333363

00:00:07.359 --> 00:00:09.360 Our speaker, Joe Chichon or

NOTE Confidence: 0.87333363

00:00:09.440 --> 00:00:11.139 I'm sorry. Chichon Sichon?

NOTE Confidence: 0.7936452

00:00:12.240 --> 00:00:12.740 Shishon.

NOTE Confidence: 0.95470303

00:00:13.405 --> 00:00:14.785 Sishon. I apologize.

NOTE Confidence: 0.65022093

00:00:15.085 --> 00:00:15.644 I'm sorry.

NOTE Confidence: 0.9701688

00:00:16.125 --> 00:00:16.625 Was,

NOTE Confidence: 0.9334552

00:00:17.404 --> 00:00:19.404 suggested and invited by, Pasha

NOTE Confidence: 0.9334552

00:00:19.404 --> 00:00:20.685 Davoodian, and I wanna invite

NOTE Confidence: 0.9334552

00:00:20.685 --> 00:00:22.224 Pasha to introduce the speaker.

NOTE Confidence: 0.99705523

00:00:23.805 --> 00:00:24.545 Thanks, Chris.

NOTE Confidence: 0.9450998

00:00:24.925 --> 00:00:26.460 Yeah. So we're very excited

NOTE Confidence: 0.9450998

00:00:26.460 --> 00:00:28.619 to have, Joe Sichon, MD

NOTE Confidence: 0.9450998

00:00:28.619 --> 00:00:30.560 PhD, assistant professor of anesthesia

NOTE Confidence: 0.9368107

00:00:31.099 --> 00:00:32.780 and neuroscience from UPenn here

NOTE Confidence: 0.9368107

00:00:32.780 --> 00:00:33.280 today.

NOTE Confidence: 0.89785355

00:00:33.899 --> 00:00:35.100 He earned his MD PhD

NOTE Confidence: 0.89785355

00:00:35.100 --> 00:00:36.720 at NYU working with one,

NOTE Confidence: 0.99216586

00:00:37.579 --> 00:00:38.780 doing some, like, really nice

NOTE Confidence: 0.99216586

00:00:38.780 --> 00:00:40.640 fundamental work on dendritic mechanisms

NOTE Confidence: 0.99216586

00:00:40.699 --> 00:00:41.760 of learning and memory.

NOTE Confidence: 0.9720506

00:00:42.524 --> 00:00:43.245 He then went on to

NOTE Confidence: 0.9720506

00:00:43.245 --> 00:00:44.304 complete an anesthesia

NOTE Confidence: 0.9645248

00:00:44.684 --> 00:00:46.765 residency at Penn, including, a

NOTE Confidence: 0.9645248

00:00:46.765 --> 00:00:48.065 research focus

NOTE Confidence: 0.96365106

00:00:48.445 --> 00:00:49.725 where he has since stayed

NOTE Confidence: 0.96365106

00:00:49.725 --> 00:00:51.265 on as an assistant professor.

NOTE Confidence: 0.9509558

00:00:51.964 --> 00:00:53.245 His main focus so far

NOTE Confidence: 0.9509558

00:00:53.245 --> 00:00:54.765 has been on rapid acting

NOTE Confidence: 0.9509558

00:00:54.765 --> 00:00:56.450 anesthetics as well as psychedelics

NOTE Confidence: 0.9509558

00:00:56.510 --> 00:00:57.790 and how they modulate neural

NOTE Confidence: 0.9509558

00:00:57.790 --> 00:00:59.170 circuits and health and disease

NOTE Confidence: 0.8893008

00:00:59.870 --> 00:01:00.910 with the goal of informing

NOTE Confidence: 0.8893008

00:01:00.910 --> 00:01:01.650 next generation,

NOTE Confidence: 0.9964656

00:01:02.030 --> 00:01:03.630 treatments for both anesthesia and

NOTE Confidence: 0.9964656

00:01:03.630 --> 00:01:04.130 antidepressants.

NOTE Confidence: 0.9127675

00:01:04.750 --> 00:01:06.030 In today's talk, he'll mostly

NOTE Confidence: 0.9127675

00:01:06.030 --> 00:01:07.890 talk about NMDA receptor antagonism

NOTE Confidence: 0.9127675

00:01:08.110 --> 00:01:09.390 work in aesthetics that he's

NOTE Confidence: 0.9127675

00:01:09.390 --> 00:01:09.890 done,

NOTE Confidence: 0.92547673

00:01:10.315 --> 00:01:11.915 in changing otherwise treatment resistant

NOTE Confidence: 0.92547673

00:01:11.915 --> 00:01:12.415 neuropsychiatric

NOTE Confidence: 0.9989891

00:01:12.795 --> 00:01:13.295 diseases.

NOTE Confidence: 0.9695251

00:01:14.155 --> 00:01:15.435 He uses several state of

NOTE Confidence: 0.9695251

00:01:15.435 --> 00:01:16.875 the art imaging approaches that

NOTE Confidence: 0.9695251

00:01:16.875 --> 00:01:18.155 are very unique and enable

NOTE Confidence: 0.9695251

00:01:18.155 --> 00:01:19.435 real time measurement of neural

NOTE Confidence: 0.9695251

00:01:19.435 --> 00:01:21.035 physiology during drug treatment at

NOTE Confidence: 0.9695251

00:01:21.035 --> 00:01:22.075 the level of single neurons,

NOTE Confidence: 0.9695251

00:01:22.075 --> 00:01:22.875 but also at the level

NOTE Confidence: 0.9695251

00:01:22.875 --> 00:01:23.535 of networks

NOTE Confidence: 0.9140476

00:01:23.890 --> 00:01:25.810 and synapses and, some really

NOTE Confidence: 0.9140476

00:01:25.810 --> 00:01:27.670 nice work hopefully illustrating how,

NOTE Confidence: 0.9025387

00:01:28.210 --> 00:01:29.569 mechanisms of ketamine and nature's

NOTE Confidence: 0.9025387

00:01:29.569 --> 00:01:31.490 oxide oxide engage in some

NOTE Confidence: 0.9025387

00:01:31.490 --> 00:01:33.190 distinct cellular and circuit level

NOTE Confidence: 0.9025387

00:01:33.330 --> 00:01:35.190 mechanisms to drive their respective

NOTE Confidence: 0.9025387

00:01:35.330 --> 00:01:36.310 rapid acting

NOTE Confidence: 0.98287576

00:01:36.865 --> 00:01:37.905 effects. So with that, I

NOTE Confidence: 0.98287576

00:01:37.905 --> 00:01:38.705 will not take any more

NOTE Confidence: 0.98287576

00:01:38.705 --> 00:01:39.825 time. The floor is yours,

NOTE Confidence: 0.98287576

00:01:39.825 --> 00:01:40.325 Joe.

NOTE Confidence: 0.9736448

00:01:41.185 --> 00:01:42.625 Thank you so much. Thank

NOTE Confidence: 0.9736448

00:01:42.625 --> 00:01:44.485 you to the Yale, Psychedelic

NOTE Confidence: 0.9736448

00:01:44.545 --> 00:01:45.045 Center,

NOTE Confidence: 0.9732916

00:01:45.425 --> 00:01:47.105 and Pasha for extending this

NOTE Confidence: 0.9732916

00:01:47.105 --> 00:01:48.545 invitation. This is truly a

NOTE Confidence: 0.9732916

00:01:48.545 --> 00:01:49.045 pleasure,

NOTE Confidence: 0.776728

00:01:50.390 --> 00:01:51.270 and I am I am

NOTE Confidence: 0.776728

00:01:51.270 --> 00:01:51.770 very

NOTE Confidence: 0.8786615

00:01:52.470 --> 00:01:54.090 overwhelmed by the invitation.

NOTE Confidence: 0.86675525

00:01:55.750 --> 00:01:56.250 So,

NOTE Confidence: 0.96953046

00:01:57.509 --> 00:01:58.710 with that, I, you know,

NOTE Confidence: 0.96953046

00:01:58.710 --> 00:02:00.229 I have no financial disclosures,

NOTE Confidence: 0.96953046

00:02:00.229 --> 00:02:01.750 but the one true disclosure

NOTE Confidence: 0.96953046

00:02:01.750 --> 00:02:02.869 is that I'm very much

NOTE Confidence: 0.96953046

00:02:02.869 --> 00:02:04.905 still in the lab doing,

NOTE Confidence: 0.9579264

00:02:05.304 --> 00:02:06.924 experiments on a daily basis,

NOTE Confidence: 0.87042934

00:02:07.465 --> 00:02:09.224 and I am briefly,

NOTE Confidence: 0.8597238

00:02:09.785 --> 00:02:10.845 completely engaged,

NOTE Confidence: 0.98166406

00:02:11.224 --> 00:02:12.665 in the data, and I've

NOTE Confidence: 0.98166406

00:02:12.665 --> 00:02:13.625 been told that I tend

NOTE Confidence: 0.98166406

00:02:13.625 --> 00:02:14.665 to present as if I'm

NOTE Confidence: 0.98166406

00:02:14.665 --> 00:02:16.105 a graduate student giving a

NOTE Confidence: 0.98166406

00:02:16.105 --> 00:02:16.925 data blitz.

NOTE Confidence: 0.9949829

00:02:17.490 --> 00:02:19.410 So, with that said, I

NOTE Confidence: 0.9949829

00:02:19.410 --> 00:02:21.250 will, try my best to

NOTE Confidence: 0.9949829

00:02:21.250 --> 00:02:23.490 not get, completely captivated by

NOTE Confidence: 0.9949829

00:02:23.490 --> 00:02:24.070 the data.

NOTE Confidence: 0.99974847

00:02:25.010 --> 00:02:26.690 So the lab is very

NOTE Confidence: 0.99974847

00:02:26.690 --> 00:02:28.150 much interested in how

NOTE Confidence: 0.9907789

00:02:28.530 --> 00:02:30.770 anesthetics with psychedelic properties and

NOTE Confidence: 0.9907789

00:02:30.770 --> 00:02:32.635 also psychedelics themselves

NOTE Confidence: 0.92476976

00:02:32.935 --> 00:02:33.435 induce,

NOTE Confidence: 0.9887809

00:02:35.335 --> 00:02:36.395 rapid and durable,

NOTE Confidence: 0.9227336

00:02:37.495 --> 00:02:37.995 corticoplasticity

NOTE Confidence: 0.95893407

00:02:38.615 --> 00:02:39.115 mechanisms.

NOTE Confidence: 0.99557894

00:02:39.975 --> 00:02:41.014 And I think many of

NOTE Confidence: 0.99557894

00:02:41.014 --> 00:02:43.195 you are also really interested

NOTE Confidence: 0.99557894

00:02:43.255 --> 00:02:44.820 in how certain drugs that

NOTE Confidence: 0.99557894

00:02:44.820 --> 00:02:45.940 are given for a very,

NOTE Confidence: 0.99557894

00:02:45.940 --> 00:02:47.320 very transient duration

NOTE Confidence: 0.9672107

00:02:48.020 --> 00:02:48.520 induce

NOTE Confidence: 0.9955775

00:02:48.900 --> 00:02:51.220 rather long lived responses in

NOTE Confidence: 0.9955775

00:02:51.220 --> 00:02:53.080 the brain, whether that's symptomatic

NOTE Confidence: 0.9955775

00:02:53.300 --> 00:02:54.919 improvements related to depression

NOTE Confidence: 0.9728794

00:02:55.380 --> 00:02:55.880 or

NOTE Confidence: 0.9931348

00:02:56.264 --> 00:02:58.204 behavioral changes that are beneficial,

NOTE Confidence: 0.98396826

00:02:58.825 --> 00:02:59.805 to the individual.

NOTE Confidence: 0.93860704

00:03:01.064 --> 00:03:02.665 How these drugs, such as

NOTE Confidence: 0.93860704

00:03:02.665 --> 00:03:03.165 ketamine,

NOTE Confidence: 0.8080854

00:03:04.985 --> 00:03:07.544 no, historically nitrous oxide, but,

NOTE Confidence: 0.8080854

00:03:07.544 --> 00:03:09.325 again, reemerging as an rapid

NOTE Confidence: 0.8080854

00:03:09.465 --> 00:03:09.965 anti

NOTE Confidence: 0.73573685

00:03:10.345 --> 00:03:10.845 antidepressant,

NOTE Confidence: 0.90987587

00:03:12.580 --> 00:03:14.840 and and psilocybin, LSD alike.

NOTE Confidence: 0.90987587

00:03:15.060 --> 00:03:16.120 How can they induce,

NOTE Confidence: 0.957057

00:03:16.580 --> 00:03:18.180 such rapid changes in neural

NOTE Confidence: 0.957057

00:03:18.180 --> 00:03:19.860 activity and changes in brain

NOTE Confidence: 0.957057

00:03:19.860 --> 00:03:21.220 state and how this sets

NOTE Confidence: 0.957057

00:03:21.220 --> 00:03:21.720 up,

NOTE Confidence: 0.9263001

00:03:22.419 --> 00:03:23.639 these these interesting,

NOTE Confidence: 0.9451448

00:03:24.675 --> 00:03:26.215 behavioral features and symptomatic,

NOTE Confidence: 0.99008095

00:03:27.395 --> 00:03:27.895 improvements.

NOTE Confidence: 0.99173903

00:03:28.995 --> 00:03:30.275 And so the the working

NOTE Confidence: 0.99173903

00:03:30.275 --> 00:03:31.735 hypothesis for how,

NOTE Confidence: 0.9610849

00:03:33.475 --> 00:03:34.535 this all happens,

NOTE Confidence: 0.99126464

00:03:36.115 --> 00:03:37.635 for my lab is related

NOTE Confidence: 0.99126464

00:03:37.635 --> 00:03:38.375 to activity

NOTE Confidence: 0.9167115

00:03:38.820 --> 00:03:40.360 dependent synaptic plasticity,

NOTE Confidence: 0.9781668

00:03:41.140 --> 00:03:42.580 and that changes in neural

NOTE Confidence: 0.9781668

00:03:42.580 --> 00:03:43.080 activity

NOTE Confidence: 0.8610964

00:03:43.620 --> 00:03:44.120 induce,

NOTE Confidence: 0.6143563

00:03:46.980 --> 00:03:47.480 distinct,

NOTE Confidence: 0.75615627

00:03:48.020 --> 00:03:48.520 receptors,

NOTE Confidence: 0.9995022

00:03:49.220 --> 00:03:49.720 engagement

NOTE Confidence: 0.88879824

00:03:50.020 --> 00:03:52.260 leading to, calcium entry, for

NOTE Confidence: 0.88879824

00:03:52.260 --> 00:03:52.760 example,

NOTE Confidence: 0.9995728

00:03:53.185 --> 00:03:54.864 leading to changes in gene

NOTE Confidence: 0.9995728

00:03:54.864 --> 00:03:55.364 expression,

NOTE Confidence: 0.99668837

00:03:55.665 --> 00:03:56.805 changes in kinase,

NOTE Confidence: 0.9942719

00:03:57.265 --> 00:03:59.525 leading to restructuring of cytoskeleton,

NOTE Confidence: 0.9788181

00:04:00.224 --> 00:04:01.504 and potentially the birth of

NOTE Confidence: 0.9788181

00:04:01.504 --> 00:04:02.165 new connections.

NOTE Confidence: 0.9929427

00:04:02.784 --> 00:04:03.525 And what's

NOTE Confidence: 0.99982756

00:04:04.144 --> 00:04:05.825 really fascinating is that these

NOTE Confidence: 0.99982756

00:04:05.825 --> 00:04:06.564 types of

NOTE Confidence: 0.90073603

00:04:06.870 --> 00:04:08.470 changes occur over different time

NOTE Confidence: 0.90073603

00:04:08.470 --> 00:04:08.970 scales,

NOTE Confidence: 0.9906363

00:04:09.430 --> 00:04:10.810 and how these drugs,

NOTE Confidence: 0.99960065

00:04:11.110 --> 00:04:12.250 that we find interesting

NOTE Confidence: 0.96374065

00:04:12.790 --> 00:04:14.230 induce these changes in these

NOTE Confidence: 0.96374065

00:04:14.230 --> 00:04:15.990 distinct steps is is is

NOTE Confidence: 0.96374065

00:04:15.990 --> 00:04:17.130 still rather unclear.

NOTE Confidence: 0.94138837

00:04:18.230 --> 00:04:19.110 And the way in which

NOTE Confidence: 0.94138837

00:04:19.110 --> 00:04:20.710 the lab has addressed, some

NOTE Confidence: 0.94138837

00:04:20.710 --> 00:04:21.270 of these,

NOTE Confidence: 0.78406155

00:04:24.385 --> 00:04:24.885 preclinical

NOTE Confidence: 0.8936763

00:04:25.265 --> 00:04:26.565 models using mouse,

NOTE Confidence: 0.9366447

00:04:27.025 --> 00:04:28.485 largely because we have

NOTE Confidence: 0.92626023

00:04:28.865 --> 00:04:30.245 access to unique cell types.

NOTE Confidence: 0.92626023

00:04:30.545 --> 00:04:32.165 We can understand connectivity,

NOTE Confidence: 0.92129093

00:04:32.689 --> 00:04:34.785 at the level of individual

NOTE Confidence: 0.92129093

00:04:34.785 --> 00:04:36.645 neurons and even local circuits,

NOTE Confidence: 0.92129093

00:04:36.945 --> 00:04:37.525 and then

NOTE Confidence: 0.9809276

00:04:38.169 --> 00:04:39.770 and we can also then,

NOTE Confidence: 0.9787651

00:04:40.250 --> 00:04:40.750 modulate,

NOTE Confidence: 0.9705394

00:04:41.210 --> 00:04:42.750 many of these distinct cells

NOTE Confidence: 0.9705394

00:04:43.050 --> 00:04:44.270 and and see their,

NOTE Confidence: 0.97021663

00:04:45.050 --> 00:04:45.550 consequences,

NOTE Confidence: 0.99896145

00:04:46.409 --> 00:04:48.089 to to circuit function and

NOTE Confidence: 0.99896145

00:04:48.089 --> 00:04:48.589 behavior.

NOTE Confidence: 0.92801255

00:04:51.735 --> 00:04:53.915 And my lab really got

NOTE Confidence: 0.92801255

00:04:54.134 --> 00:04:54.634 hooked,

NOTE Confidence: 0.88529533

00:04:55.815 --> 00:04:56.634 into this,

NOTE Confidence: 0.99975276

00:04:57.654 --> 00:04:58.714 outstanding question

NOTE Confidence: 0.932271

00:05:00.775 --> 00:05:02.214 and and and and thinking

NOTE Confidence: 0.932271

00:05:02.214 --> 00:05:04.455 about this was through work,

NOTE Confidence: 0.932271

00:05:04.615 --> 00:05:06.960 done, you know, largely at

NOTE Confidence: 0.932271

00:05:06.960 --> 00:05:08.419 Yale and at the NIH,

NOTE Confidence: 0.99434394

00:05:09.599 --> 00:05:10.099 where,

NOTE Confidence: 0.9591713

00:05:10.880 --> 00:05:12.160 you know, two separate groups

NOTE Confidence: 0.9591713

00:05:12.160 --> 00:05:12.660 independently,

NOTE Confidence: 0.84779835

00:05:14.000 --> 00:05:15.460 determined that subantanacetamin

NOTE Confidence: 0.9778301

00:05:16.000 --> 00:05:16.800 so this is not an

NOTE Confidence: 0.9778301

00:05:16.800 --> 00:05:18.500 anesthetic dose of ketamin. Subantanacetamin

NOTE Confidence: 0.96987575

00:05:18.960 --> 00:05:20.475 given over forty minutes to

NOTE Confidence: 0.96987575

00:05:20.475 --> 00:05:22.955 an hour induces a rapid

NOTE Confidence: 0.96987575

00:05:22.955 --> 00:05:24.735 change in, antidepressant

NOTE Confidence: 0.9998379

00:05:25.035 --> 00:05:25.535 symptoms

NOTE Confidence: 0.98841476

00:05:25.915 --> 00:05:27.595 that emerge within minutes upon

NOTE Confidence: 0.98841476

00:05:27.595 --> 00:05:29.055 completing, the infusion.

NOTE Confidence: 0.95148355

00:05:30.635 --> 00:05:31.935 And you can see here,

NOTE Confidence: 0.9821101

00:05:33.639 --> 00:05:35.260 that there's a distinct separation

NOTE Confidence: 0.9821101

00:05:35.400 --> 00:05:36.680 between the placebo group and

NOTE Confidence: 0.9821101

00:05:36.680 --> 00:05:38.460 the ketamine group that,

NOTE Confidence: 0.900475

00:05:38.920 --> 00:05:39.420 spans,

NOTE Confidence: 0.9823538

00:05:39.800 --> 00:05:41.400 within the first day of

NOTE Confidence: 0.9823538

00:05:41.400 --> 00:05:43.240 receiving the treatment, and that

NOTE Confidence: 0.9823538

00:05:43.240 --> 00:05:43.740 lasts,

NOTE Confidence: 0.96004254

00:05:44.120 --> 00:05:45.720 for multiple days, if not

NOTE Confidence: 0.96004254

00:05:45.720 --> 00:05:46.940 weeks, in some patients.

NOTE Confidence: 0.9722768

00:05:48.835 --> 00:05:50.514 And this is, you know,

NOTE Confidence: 0.9722768

00:05:50.514 --> 00:05:52.615 amazing considering that this was,

NOTE Confidence: 0.9998088

00:05:53.074 --> 00:05:54.134 initially classified

NOTE Confidence: 0.99456483

00:05:54.514 --> 00:05:55.574 as an anesthetic.

NOTE Confidence: 0.9477198

00:05:57.235 --> 00:05:58.354 And what I found really

NOTE Confidence: 0.9477198

00:05:58.354 --> 00:05:59.634 unique, just given my,

NOTE Confidence: 0.9543019

00:06:01.419 --> 00:06:02.720 clinical training in anesthesia,

NOTE Confidence: 0.8773279

00:06:03.259 --> 00:06:04.000 is that,

NOTE Confidence: 0.9344372

00:06:04.620 --> 00:06:06.460 indeed, during this infusion, this

NOTE Confidence: 0.9344372

00:06:06.460 --> 00:06:08.300 sub hypnotic infusion, the patient's

NOTE Confidence: 0.9344372

00:06:08.300 --> 00:06:10.460 not anesthetized. They're able to

NOTE Confidence: 0.9344372

00:06:10.460 --> 00:06:10.960 respond.

NOTE Confidence: 0.94730705

00:06:11.819 --> 00:06:13.500 They experience a unique state,

NOTE Confidence: 0.94730705

00:06:13.500 --> 00:06:14.800 which we call disassociation.

NOTE Confidence: 0.97266257

00:06:15.259 --> 00:06:16.654 And it's, in fact, it's

NOTE Confidence: 0.97266257

00:06:16.714 --> 00:06:18.714 this property that gave ketamine

NOTE Confidence: 0.97266257

00:06:18.714 --> 00:06:20.414 the classification as a disassociated

NOTE Confidence: 0.9794461

00:06:20.714 --> 00:06:21.214 anesthetic

NOTE Confidence: 0.93821037

00:06:21.754 --> 00:06:23.595 because at these subanesthetic doses,

NOTE Confidence: 0.93821037

00:06:23.595 --> 00:06:24.654 it has this profound,

NOTE Confidence: 0.9686776

00:06:27.194 --> 00:06:28.634 induction of a different brain

NOTE Confidence: 0.9686776

00:06:28.634 --> 00:06:30.210 state. And what what I

NOTE Confidence: 0.9686776

00:06:30.210 --> 00:06:31.110 mean by disassociation

NOTE Confidence: 0.9748689

00:06:31.650 --> 00:06:33.430 is that it, it distorts,

NOTE Confidence: 0.8776394

00:06:34.770 --> 00:06:35.670 various different,

NOTE Confidence: 0.9963199

00:06:36.370 --> 00:06:36.870 percepts

NOTE Confidence: 0.8742474

00:06:37.170 --> 00:06:38.550 of of the world. It

NOTE Confidence: 0.8742474

00:06:38.610 --> 00:06:40.310 it distorts the your

NOTE Confidence: 0.98883873

00:06:40.770 --> 00:06:42.230 representation of body.

NOTE Confidence: 0.95912725

00:06:42.845 --> 00:06:44.205 It disconnects you from your

NOTE Confidence: 0.95912725

00:06:44.205 --> 00:06:46.305 environment, disconnects you from time.

NOTE Confidence: 0.9979308

00:06:47.485 --> 00:06:48.225 You become

NOTE Confidence: 0.9528068

00:06:48.685 --> 00:06:49.185 depersonalized,

NOTE Confidence: 0.89625555

00:06:49.645 --> 00:06:51.404 you realize, and you start

NOTE Confidence: 0.89625555

00:06:51.404 --> 00:06:52.065 to experience,

NOTE Confidence: 0.75351655

00:06:53.005 --> 00:06:53.485 even,

NOTE Confidence: 0.9614043

00:06:53.964 --> 00:06:55.964 illusions or hallucinations. And that

NOTE Confidence: 0.9614043

00:06:55.964 --> 00:06:58.089 this experience is often just

NOTE Confidence: 0.9614043

00:06:58.089 --> 00:06:59.449 tied to the drug exposure,

NOTE Confidence: 0.9614043

00:06:59.449 --> 00:06:59.949 maybe,

NOTE Confidence: 0.98052055

00:07:01.130 --> 00:07:03.130 trickles into periods after the,

NOTE Confidence: 0.98052055

00:07:03.610 --> 00:07:04.509 drug exposure,

NOTE Confidence: 0.9634515

00:07:04.889 --> 00:07:06.669 but it's eventually resolved,

NOTE Confidence: 0.98016775

00:07:07.210 --> 00:07:09.069 once the drug is supposedly,

NOTE Confidence: 0.99721414

00:07:10.090 --> 00:07:11.150 cleared and metabolized.

NOTE Confidence: 0.99374926

00:07:12.795 --> 00:07:14.395 And I'm gonna revisit this

NOTE Confidence: 0.99374926

00:07:14.395 --> 00:07:15.775 whole idea of this association.

NOTE Confidence: 0.99374926

00:07:15.915 --> 00:07:16.955 And so this was a

NOTE Confidence: 0.99374926

00:07:16.955 --> 00:07:19.275 remarkable finding because ketamine in

NOTE Confidence: 0.99374926

00:07:19.275 --> 00:07:21.755 this patient population did nearly

NOTE Confidence: 0.99374926

00:07:21.755 --> 00:07:24.075 twice as good as standard

NOTE Confidence: 0.99374926

00:07:24.075 --> 00:07:24.875 of care, which would be

NOTE Confidence: 0.99374926

00:07:24.875 --> 00:07:25.615 an SSRI.

NOTE Confidence: 0.9403727

00:07:26.235 --> 00:07:27.515 And in fact, it's really

NOTE Confidence: 0.9403727

00:07:27.515 --> 00:07:28.015 the

NOTE Confidence: 0.9940537

00:07:28.370 --> 00:07:30.129 single application of ketamine that

NOTE Confidence: 0.9940537

00:07:30.129 --> 00:07:31.270 was doing this,

NOTE Confidence: 0.98020613

00:07:34.210 --> 00:07:34.710 effect.

NOTE Confidence: 0.9740402

00:07:35.569 --> 00:07:36.449 And as a as a

NOTE Confidence: 0.9740402

00:07:36.449 --> 00:07:38.710 basic scientist, I I began

NOTE Confidence: 0.9740402

00:07:38.770 --> 00:07:39.970 to gauge literature and try

NOTE Confidence: 0.9740402

00:07:39.970 --> 00:07:41.650 to figure out exactly what

NOTE Confidence: 0.9740402

00:07:41.650 --> 00:07:43.349 people thought of how these

NOTE Confidence: 0.9983531

00:07:44.725 --> 00:07:45.925 rapid and sort of more

NOTE Confidence: 0.9983531

00:07:45.925 --> 00:07:46.985 durable effects

NOTE Confidence: 0.99532807

00:07:47.605 --> 00:07:48.425 are happening.

NOTE Confidence: 0.9915954

00:07:49.205 --> 00:07:49.705 And,

NOTE Confidence: 0.98262554

00:07:50.085 --> 00:07:51.685 I'm gonna make this very

NOTE Confidence: 0.98262554

00:07:51.685 --> 00:07:53.285 superficial, but the thinking is

NOTE Confidence: 0.98262554

00:07:53.285 --> 00:07:55.045 is that ketamine is an,

NOTE Confidence: 0.98262554

00:07:55.365 --> 00:07:58.005 NMDA blocker specifically targeting open,

NOTE Confidence: 0.98262554

00:07:58.245 --> 00:07:59.385 NMDA channels,

NOTE Confidence: 0.9833667

00:08:00.110 --> 00:08:02.830 and, this blockade preferentially happens

NOTE Confidence: 0.9833667

00:08:02.830 --> 00:08:04.289 on GABAergic interneurons

NOTE Confidence: 0.9280208

00:08:05.069 --> 00:08:06.669 leading to a suppression of

NOTE Confidence: 0.9280208

00:08:06.669 --> 00:08:07.810 interneuron activity

NOTE Confidence: 0.9984114

00:08:08.430 --> 00:08:09.409 that would subsequently

NOTE Confidence: 0.9997398

00:08:09.789 --> 00:08:10.289 drive

NOTE Confidence: 0.9998892

00:08:11.069 --> 00:08:11.569 excitatory

NOTE Confidence: 0.9887948

00:08:11.870 --> 00:08:12.370 activity.

NOTE Confidence: 0.9384772

00:08:13.355 --> 00:08:15.675 Excitatory activity dumping glutamate would

NOTE Confidence: 0.9384772

00:08:15.675 --> 00:08:17.695 then drive in subsequent cells,

NOTE Confidence: 0.9827882

00:08:18.795 --> 00:08:19.775 signaling changes,

NOTE Confidence: 0.93030685

00:08:20.395 --> 00:08:23.055 protein gene expression, protein expression,

NOTE Confidence: 0.93030685

00:08:23.275 --> 00:08:24.015 and potentially

NOTE Confidence: 0.9846634

00:08:24.475 --> 00:08:25.775 new synapse formation.

NOTE Confidence: 0.9160398

00:08:26.830 --> 00:08:27.870 So with these sort of

NOTE Confidence: 0.9160398

00:08:27.870 --> 00:08:29.650 activity changes underlying the initiating

NOTE Confidence: 0.9160398

00:08:29.710 --> 00:08:30.210 mechanisms

NOTE Confidence: 0.94080234

00:08:30.510 --> 00:08:32.590 followed by new formation of

NOTE Confidence: 0.94080234

00:08:32.590 --> 00:08:33.090 synapse

NOTE Confidence: 0.40581042

00:08:33.790 --> 00:08:34.290 underlying

NOTE Confidence: 0.97382426

00:08:34.750 --> 00:08:36.290 the sustaining mechanisms.

NOTE Confidence: 0.9992798

00:08:38.030 --> 00:08:39.490 If you follow this logic,

NOTE Confidence: 0.9945051

00:08:40.014 --> 00:08:41.475 then you might think, well,

NOTE Confidence: 0.9945051

00:08:41.535 --> 00:08:42.654 maybe we can do better

NOTE Confidence: 0.9945051

00:08:42.654 --> 00:08:44.175 than ketamine. Maybe we can

NOTE Confidence: 0.9945051

00:08:44.175 --> 00:08:45.635 design out the disassociation

NOTE Confidence: 0.9646732

00:08:46.014 --> 00:08:46.995 with very specific,

NOTE Confidence: 0.92324907

00:08:47.695 --> 00:08:49.714 NMD antagonists or NMD modulators.

NOTE Confidence: 0.90430236

00:08:50.095 --> 00:08:50.834 And indeed,

NOTE Confidence: 0.93351537

00:08:52.059 --> 00:08:52.960 you know, academics

NOTE Confidence: 0.98341304

00:08:53.340 --> 00:08:55.040 and and and pharma companies

NOTE Confidence: 0.98341304

00:08:55.100 --> 00:08:56.880 have thought deeply about this

NOTE Confidence: 0.84878385

00:08:57.420 --> 00:08:59.760 question and have, engineered,

NOTE Confidence: 0.9983984

00:09:00.140 --> 00:09:01.680 you know, amazing compounds

NOTE Confidence: 0.96420026

00:09:02.220 --> 00:09:03.980 that in preclinical models show

NOTE Confidence: 0.96420026

00:09:03.980 --> 00:09:05.900 efficacy, but in in in

NOTE Confidence: 0.96420026

00:09:05.900 --> 00:09:06.400 human

NOTE Confidence: 0.82358485

00:09:07.605 --> 00:09:09.145 trials, just fall short.

NOTE Confidence: 0.8777664

00:09:10.165 --> 00:09:10.904 And so,

NOTE Confidence: 0.97635686

00:09:11.365 --> 00:09:13.684 acknowledging all these efforts, through

NOTE Confidence: 0.97635686

00:09:13.684 --> 00:09:15.365 the years, I thought about

NOTE Confidence: 0.97635686

00:09:15.365 --> 00:09:16.985 this question slightly different.

NOTE Confidence: 0.9303988

00:09:17.925 --> 00:09:19.684 And this was also motivated

NOTE Confidence: 0.9303988

00:09:19.684 --> 00:09:20.885 by a bunch of papers

NOTE Confidence: 0.9303988

00:09:20.885 --> 00:09:22.920 coming, subsequently from the the

NOTE Confidence: 0.9303988

00:09:22.920 --> 00:09:23.420 Zarate

NOTE Confidence: 0.967183

00:09:24.200 --> 00:09:25.580 group, at the NIH

NOTE Confidence: 0.883899

00:09:26.120 --> 00:09:27.500 where they found an association

NOTE Confidence: 0.883899

00:09:27.800 --> 00:09:29.100 between the dissociative

NOTE Confidence: 0.9878735

00:09:29.559 --> 00:09:31.080 state and the fact that

NOTE Confidence: 0.9878735

00:09:31.080 --> 00:09:32.440 if you experience this state,

NOTE Confidence: 0.9878735

00:09:32.440 --> 00:09:33.480 you might have a more

NOTE Confidence: 0.9878735

00:09:33.480 --> 00:09:35.100 robust sustained antidepressant

NOTE Confidence: 0.9980198

00:09:35.480 --> 00:09:35.980 response.

NOTE Confidence: 0.98576826

00:09:37.695 --> 00:09:39.554 And so I was curious,

NOTE Confidence: 0.98576826

00:09:39.615 --> 00:09:40.735 in a mouse, can we

NOTE Confidence: 0.98576826

00:09:40.735 --> 00:09:42.595 determine when that happens?

NOTE Confidence: 0.9994141

00:09:43.214 --> 00:09:44.815 And so I devised a

NOTE Confidence: 0.9994141

00:09:44.815 --> 00:09:47.054 series of behavioral experiments to

NOTE Confidence: 0.9994141

00:09:47.054 --> 00:09:48.195 see if I can pinpoint

NOTE Confidence: 0.9994141

00:09:48.415 --> 00:09:50.115 exactly where a mouse becomes

NOTE Confidence: 0.99132276

00:09:51.820 --> 00:09:52.320 disassociated.

NOTE Confidence: 0.94820565

00:09:52.700 --> 00:09:53.900 So so here you have

NOTE Confidence: 0.94820565

00:09:53.900 --> 00:09:54.480 a mouse

NOTE Confidence: 0.9704194

00:09:54.940 --> 00:09:56.620 in tail suspension. Tail suspension

NOTE Confidence: 0.9704194

00:09:56.620 --> 00:09:58.240 is often used as a,

NOTE Confidence: 0.9983579

00:09:58.780 --> 00:10:00.620 behavioral test to assess for

NOTE Confidence: 0.9983579

00:10:00.620 --> 00:10:01.360 learned helplessness.

NOTE Confidence: 0.97195274

00:10:01.900 --> 00:10:02.940 Here you have a mouse

NOTE Confidence: 0.97195274

00:10:02.940 --> 00:10:04.240 hanging by its tail,

NOTE Confidence: 0.9805874

00:10:04.755 --> 00:10:06.195 very commonly done, and you

NOTE Confidence: 0.9805874

00:10:06.195 --> 00:10:07.315 see that the mouse attempts

NOTE Confidence: 0.9805874

00:10:07.315 --> 00:10:08.195 to escape, and they do

NOTE Confidence: 0.9805874

00:10:08.195 --> 00:10:08.915 this for a period of

NOTE Confidence: 0.9805874

00:10:08.915 --> 00:10:10.055 time. This is considered,

NOTE Confidence: 0.8720067

00:10:10.595 --> 00:10:12.455 mobility, and then it interdispersed

NOTE Confidence: 0.8720067

00:10:12.755 --> 00:10:13.255 between,

NOTE Confidence: 0.9899642

00:10:13.715 --> 00:10:15.315 active escape events. You have

NOTE Confidence: 0.9899642

00:10:15.315 --> 00:10:16.835 these periods of immobility where

NOTE Confidence: 0.9899642

00:10:16.835 --> 00:10:17.495 the mice,

NOTE Confidence: 0.9649949

00:10:18.035 --> 00:10:19.335 sort of just give up,

NOTE Confidence: 0.9649949

00:10:19.395 --> 00:10:20.010 and and then they have

NOTE Confidence: 0.9649949

00:10:20.010 --> 00:10:21.610 a resurgence of wanting to

NOTE Confidence: 0.9649949

00:10:21.610 --> 00:10:24.090 escape and try to, curl

NOTE Confidence: 0.9649949

00:10:24.090 --> 00:10:25.530 and and and swing and

NOTE Confidence: 0.9649949

00:10:25.530 --> 00:10:26.490 and try to get out

NOTE Confidence: 0.9649949

00:10:26.490 --> 00:10:27.950 of this uncomfortable position.

NOTE Confidence: 0.97286683

00:10:29.130 --> 00:10:30.250 And what you find here

NOTE Confidence: 0.97286683

00:10:30.250 --> 00:10:31.530 at ketamine at a certain

NOTE Confidence: 0.97286683

00:10:31.530 --> 00:10:32.970 dose, it's very high relative

NOTE Confidence: 0.97286683

00:10:32.970 --> 00:10:33.930 to humans, and we can

NOTE Confidence: 0.97286683

00:10:33.930 --> 00:10:35.295 go into that later. You

NOTE Confidence: 0.97286683

00:10:35.295 --> 00:10:36.915 find that the mouse completely

NOTE Confidence: 0.97286683

00:10:37.135 --> 00:10:38.675 loses that escape behavior.

NOTE Confidence: 0.9457879

00:10:39.695 --> 00:10:40.675 There's no,

NOTE Confidence: 0.9972806

00:10:41.135 --> 00:10:42.515 attempt to escape.

NOTE Confidence: 0.9975129

00:10:42.895 --> 00:10:44.095 In fact, they sort of

NOTE Confidence: 0.9975129

00:10:44.095 --> 00:10:44.915 hang there,

NOTE Confidence: 0.973772

00:10:45.615 --> 00:10:46.975 and you see this interesting

NOTE Confidence: 0.973772

00:10:46.975 --> 00:10:48.095 head twitch. And this is

NOTE Confidence: 0.973772

00:10:48.095 --> 00:10:50.040 very distinct from something that

NOTE Confidence: 0.973772

00:10:50.360 --> 00:10:51.720 psilocybin or LSD would do,

NOTE Confidence: 0.973772

00:10:51.720 --> 00:10:52.779 which would be a rotational

NOTE Confidence: 0.973772

00:10:52.839 --> 00:10:54.440 head twitch, and a mouse

NOTE Confidence: 0.973772

00:10:54.440 --> 00:10:55.980 was like like a dog

NOTE Confidence: 0.973772

00:10:56.279 --> 00:10:58.279 shaking off its wet, wet

NOTE Confidence: 0.973772

00:10:58.279 --> 00:10:58.779 fur

NOTE Confidence: 0.89313453

00:10:59.160 --> 00:11:00.600 to get dry. This, you

NOTE Confidence: 0.89313453

00:11:00.600 --> 00:11:01.959 see it's sort of vertical

NOTE Confidence: 0.89313453

00:11:01.959 --> 00:11:02.920 and that the how the

NOTE Confidence: 0.89313453

00:11:02.920 --> 00:11:04.485 the mouse's head sort of

NOTE Confidence: 0.89313453

00:11:04.485 --> 00:11:04.985 bobs.

NOTE Confidence: 0.9771178

00:11:06.085 --> 00:11:07.365 And interestingly, if you take

NOTE Confidence: 0.9771178

00:11:07.365 --> 00:11:08.405 that mouse out of tail

NOTE Confidence: 0.9771178

00:11:08.405 --> 00:11:10.085 suspension, they'll begin to move

NOTE Confidence: 0.9771178

00:11:10.085 --> 00:11:10.585 about.

NOTE Confidence: 0.9833968

00:11:12.405 --> 00:11:13.605 And so here's a dose

NOTE Confidence: 0.9833968

00:11:13.605 --> 00:11:15.145 response curve looking at,

NOTE Confidence: 0.96878463

00:11:15.605 --> 00:11:17.545 immobility time and tail suspension

NOTE Confidence: 0.96878463

00:11:17.684 --> 00:11:18.425 and also

NOTE Confidence: 0.86658955

00:11:18.819 --> 00:11:20.040 a head twitch response.

NOTE Confidence: 0.9770858

00:11:20.420 --> 00:11:21.459 And what you find is

NOTE Confidence: 0.9770858

00:11:21.459 --> 00:11:22.259 that once you get to

NOTE Confidence: 0.9770858

00:11:22.259 --> 00:11:23.339 a dose of fifty and

NOTE Confidence: 0.9770858

00:11:23.339 --> 00:11:24.759 a hundred mgs per kg,

NOTE Confidence: 0.9770858

00:11:24.819 --> 00:11:25.559 the mice,

NOTE Confidence: 0.99288

00:11:26.179 --> 00:11:28.500 will become completely immobile, no

NOTE Confidence: 0.99288

00:11:28.500 --> 00:11:30.259 escape behavior, and they'll also

NOTE Confidence: 0.99288

00:11:30.259 --> 00:11:31.540 have this sort of sustained

NOTE Confidence: 0.99288

00:11:31.540 --> 00:11:33.559 head twitch over this recording

NOTE Confidence: 0.99288

00:11:33.620 --> 00:11:34.120 period.

NOTE Confidence: 0.99513566

00:11:34.835 --> 00:11:36.434 To convince myself that I

NOTE Confidence: 0.99513566

00:11:36.434 --> 00:11:37.495 was looking at,

NOTE Confidence: 0.9510164

00:11:37.875 --> 00:11:39.554 disassociation, I devised a few

NOTE Confidence: 0.9510164

00:11:39.554 --> 00:11:41.235 more behavioral tests. In this

NOTE Confidence: 0.9510164

00:11:41.235 --> 00:11:42.595 behavioral test, the mouse is

NOTE Confidence: 0.9510164

00:11:42.595 --> 00:11:43.875 head fixed, and I placed

NOTE Confidence: 0.9510164

00:11:43.875 --> 00:11:45.635 an adhesive on its nose,

NOTE Confidence: 0.9510164

00:11:45.635 --> 00:11:46.675 so it's sitting on its

NOTE Confidence: 0.9510164

00:11:46.675 --> 00:11:48.515 snout, and its whiskers can

NOTE Confidence: 0.9510164

00:11:48.515 --> 00:11:49.655 also feel the adhesive.

NOTE Confidence: 0.97343475

00:11:50.429 --> 00:11:52.610 And, mice normally find this

NOTE Confidence: 0.97343475

00:11:52.750 --> 00:11:54.510 very aversive and, knock it

NOTE Confidence: 0.97343475

00:11:54.510 --> 00:11:55.710 straight away within, like, a

NOTE Confidence: 0.97343475

00:11:55.710 --> 00:11:56.690 second or two,

NOTE Confidence: 0.962099

00:11:57.390 --> 00:11:58.510 a very short period of

NOTE Confidence: 0.962099

00:11:58.510 --> 00:12:00.190 time. But with ketamine at

NOTE Confidence: 0.962099

00:12:00.190 --> 00:12:02.050 these doses, they become

NOTE Confidence: 0.9078294

00:12:02.429 --> 00:12:04.130 completely unaware of the sticker.

NOTE Confidence: 0.9638781

00:12:05.024 --> 00:12:06.865 Similarly, if you expose a

NOTE Confidence: 0.9638781

00:12:06.865 --> 00:12:08.065 mouse to a simple air

NOTE Confidence: 0.9638781

00:12:08.065 --> 00:12:08.565 puff,

NOTE Confidence: 0.9993511

00:12:09.184 --> 00:12:10.084 they have a

NOTE Confidence: 0.9645358

00:12:10.464 --> 00:12:12.464 withdrawal response, and ketamine at

NOTE Confidence: 0.9645358

00:12:12.464 --> 00:12:14.625 these, two particular doses, this

NOTE Confidence: 0.9645358

00:12:14.625 --> 00:12:16.304 modern high dose, failed to

NOTE Confidence: 0.9645358

00:12:16.304 --> 00:12:16.964 do that.

NOTE Confidence: 0.9998684

00:12:17.840 --> 00:12:18.340 Moreover,

NOTE Confidence: 0.9851988

00:12:18.720 --> 00:12:19.680 if you put a mouse

NOTE Confidence: 0.9851988

00:12:19.680 --> 00:12:21.120 in a rat's cage exposed

NOTE Confidence: 0.9851988

00:12:21.120 --> 00:12:22.480 to marbles, they have this

NOTE Confidence: 0.9851988

00:12:22.480 --> 00:12:24.160 intrinsic desire to bury these

NOTE Confidence: 0.9851988

00:12:24.160 --> 00:12:24.660 marbles,

NOTE Confidence: 0.99459773

00:12:25.200 --> 00:12:26.640 so they'll bury a fraction

NOTE Confidence: 0.99459773

00:12:26.640 --> 00:12:27.220 of them.

NOTE Confidence: 0.9609373

00:12:28.000 --> 00:12:29.520 And interestingly, if you give

NOTE Confidence: 0.9609373

00:12:29.520 --> 00:12:31.304 the mouse a a ketamine

NOTE Confidence: 0.9609373

00:12:31.605 --> 00:12:33.065 at these two different doses,

NOTE Confidence: 0.9609373

00:12:33.365 --> 00:12:34.404 they failed to bury a

NOTE Confidence: 0.9609373

00:12:34.404 --> 00:12:35.765 single marble. But if you

NOTE Confidence: 0.9609373

00:12:35.765 --> 00:12:37.524 record their movement throughout this

NOTE Confidence: 0.9609373

00:12:37.524 --> 00:12:38.345 rat's cage,

NOTE Confidence: 0.98902416

00:12:39.045 --> 00:12:40.345 they seem to be moving

NOTE Confidence: 0.98902416

00:12:40.565 --> 00:12:41.945 no different or

NOTE Confidence: 0.92440736

00:12:42.565 --> 00:12:43.945 some increase, some decrease

NOTE Confidence: 0.9728497

00:12:44.309 --> 00:12:45.850 relative to their, baseline.

NOTE Confidence: 0.9973259

00:12:46.790 --> 00:12:47.590 So it's not that the

NOTE Confidence: 0.9973259

00:12:47.590 --> 00:12:48.890 mouse is even sedated,

NOTE Confidence: 0.9927683

00:12:49.429 --> 00:12:50.490 at this particular

NOTE Confidence: 0.9522286

00:12:50.870 --> 00:12:52.010 at these two doses.

NOTE Confidence: 0.9787289

00:12:52.630 --> 00:12:53.590 When you look under the

NOTE Confidence: 0.9787289

00:12:53.590 --> 00:12:54.870 hood at the EEG, you

NOTE Confidence: 0.9787289

00:12:54.870 --> 00:12:56.230 find that ketamine at these

NOTE Confidence: 0.9787289

00:12:56.230 --> 00:12:57.350 two different doses, and these

NOTE Confidence: 0.9787289

00:12:57.350 --> 00:12:58.950 are not anesthetic doses, you

NOTE Confidence: 0.9787289

00:12:58.950 --> 00:13:00.334 couldn't perform a surgery

NOTE Confidence: 0.92554754

00:13:00.635 --> 00:13:02.014 on a mouse. You actually

NOTE Confidence: 0.92554754

00:13:02.154 --> 00:13:03.774 most likely need an adjunct

NOTE Confidence: 0.92554754

00:13:03.834 --> 00:13:04.735 like dexmedetomidine

NOTE Confidence: 0.8728986

00:13:05.834 --> 00:13:07.615 or, xylazine to reduce,

NOTE Confidence: 0.9275068

00:13:07.995 --> 00:13:09.755 an general anesthesia for a

NOTE Confidence: 0.9275068

00:13:09.755 --> 00:13:11.695 mouse. So at these subhypnoct

NOTE Confidence: 0.9275068

00:13:11.834 --> 00:13:13.054 doses I would describe,

NOTE Confidence: 0.93454427

00:13:13.509 --> 00:13:14.630 you could see these fast

NOTE Confidence: 0.93454427

00:13:14.630 --> 00:13:15.769 oscillations emerging,

NOTE Confidence: 0.9528801

00:13:17.750 --> 00:13:19.690 which is not terribly surprising.

NOTE Confidence: 0.9997453

00:13:20.149 --> 00:13:21.130 What is surprising

NOTE Confidence: 0.9997441

00:13:21.670 --> 00:13:23.209 is when you start doing

NOTE Confidence: 0.8149455

00:13:24.149 --> 00:13:24.809 two photon,

NOTE Confidence: 0.9893066

00:13:25.829 --> 00:13:26.329 imaging

NOTE Confidence: 0.94185835

00:13:27.865 --> 00:13:29.305 into the the the living

NOTE Confidence: 0.94185835

00:13:29.305 --> 00:13:30.985 mouse brain. And in these

NOTE Confidence: 0.94185835

00:13:30.985 --> 00:13:32.684 experiments, the mouse's head fixed.

NOTE Confidence: 0.9218301

00:13:32.985 --> 00:13:33.865 It's in the mouse that

NOTE Confidence: 0.9218301

00:13:33.865 --> 00:13:34.605 is expressing,

NOTE Confidence: 0.9674643

00:13:36.905 --> 00:13:37.645 thigh one.

NOTE Confidence: 0.9791473

00:13:39.385 --> 00:13:40.905 It's it's expressing GCaM under

NOTE Confidence: 0.9791473

00:13:40.905 --> 00:13:42.420 the thigh one promoter, which

NOTE Confidence: 0.9791473

00:13:42.420 --> 00:13:44.260 is labeling excitatory cells in

NOTE Confidence: 0.9791473

00:13:44.260 --> 00:13:45.940 the brain. And in these

NOTE Confidence: 0.9791473

00:13:45.940 --> 00:13:47.620 traces, you're looking at GCaMP

NOTE Confidence: 0.9791473

00:13:47.620 --> 00:13:49.540 fluorescence over time in a

NOTE Confidence: 0.9791473

00:13:49.540 --> 00:13:50.980 in a local cortical region.

NOTE Confidence: 0.9791473

00:13:50.980 --> 00:13:51.700 So this is a two

NOTE Confidence: 0.9791473

00:13:51.700 --> 00:13:53.220 dimensional slice, almost like a

NOTE Confidence: 0.9791473

00:13:53.220 --> 00:13:54.975 CT scan through the mouse's

NOTE Confidence: 0.9791473

00:13:54.975 --> 00:13:55.475 brain,

NOTE Confidence: 0.98165995

00:13:55.855 --> 00:13:57.395 and we're recording these calcium

NOTE Confidence: 0.98165995

00:13:57.695 --> 00:13:58.195 fluctuations,

NOTE Confidence: 0.9689557

00:13:58.575 --> 00:14:00.015 which are a proxy for

NOTE Confidence: 0.9689557

00:14:00.015 --> 00:14:01.695 neural activity. And so when

NOTE Confidence: 0.9689557

00:14:01.695 --> 00:14:02.735 you see a spike in

NOTE Confidence: 0.9689557

00:14:02.735 --> 00:14:04.835 calcium, that's most likely reflecting

NOTE Confidence: 0.9689557

00:14:04.895 --> 00:14:06.270 some type of action potential

NOTE Confidence: 0.24931693

00:14:10.590 --> 00:14:11.090 in

NOTE Confidence: 0.91065884

00:14:11.630 --> 00:14:13.010 you're recording this animal

NOTE Confidence: 0.87868047

00:14:13.470 --> 00:14:14.450 spontaneous activity,

NOTE Confidence: 0.9923479

00:14:14.910 --> 00:14:15.950 when you give this moderate

NOTE Confidence: 0.9923479

00:14:15.950 --> 00:14:17.090 and high dose of ketamine,

NOTE Confidence: 0.99955404

00:14:17.630 --> 00:14:19.070 you find that neurons that

NOTE Confidence: 0.99955404

00:14:19.070 --> 00:14:20.370 were previously active

NOTE Confidence: 0.9845837

00:14:21.555 --> 00:14:23.334 attenuate or even switch off,

NOTE Confidence: 0.9845837

00:14:23.394 --> 00:14:24.855 whereas cells that were previously

NOTE Confidence: 0.9845837

00:14:24.915 --> 00:14:25.415 silent,

NOTE Confidence: 0.9931345

00:14:25.795 --> 00:14:27.634 switch on. And this was

NOTE Confidence: 0.9931345

00:14:27.634 --> 00:14:28.915 surprising because when I first

NOTE Confidence: 0.9931345

00:14:28.915 --> 00:14:31.154 did the analysis, I I

NOTE Confidence: 0.9931345

00:14:31.154 --> 00:14:32.355 was looking at sort of

NOTE Confidence: 0.9931345

00:14:32.355 --> 00:14:33.954 the average activity across the

NOTE Confidence: 0.9931345

00:14:33.954 --> 00:14:35.560 two different states, and they

NOTE Confidence: 0.9931345

00:14:35.560 --> 00:14:37.560 were basically no different. But

NOTE Confidence: 0.9931345

00:14:37.560 --> 00:14:38.839 when you look at what

NOTE Confidence: 0.9931345

00:14:38.839 --> 00:14:40.199 are the neurons contributing to

NOTE Confidence: 0.9931345

00:14:40.199 --> 00:14:40.940 this activity,

NOTE Confidence: 0.918319

00:14:41.879 --> 00:14:43.259 they're completely different.

NOTE Confidence: 0.98071665

00:14:46.519 --> 00:14:47.560 And this is the summary

NOTE Confidence: 0.98071665

00:14:47.560 --> 00:14:47.835 of

NOTE Confidence: 0.95013434

00:14:48.475 --> 00:14:49.755 of of neurons recorded in

NOTE Confidence: 0.95013434

00:14:49.755 --> 00:14:51.275 this particular region. You could

NOTE Confidence: 0.95013434

00:14:51.275 --> 00:14:51.775 see

NOTE Confidence: 0.98330826

00:14:52.315 --> 00:14:53.355 there's really not much in

NOTE Confidence: 0.98330826

00:14:53.355 --> 00:14:53.995 the way of a change

NOTE Confidence: 0.98330826

00:14:53.995 --> 00:14:55.435 with saline injection, but at

NOTE Confidence: 0.98330826

00:14:55.435 --> 00:14:56.555 these two different doses of

NOTE Confidence: 0.98330826

00:14:56.555 --> 00:14:57.055 ketamine,

NOTE Confidence: 0.9820364

00:14:57.355 --> 00:14:58.475 you see that cells that

NOTE Confidence: 0.9820364

00:14:58.475 --> 00:14:59.135 were previously,

NOTE Confidence: 0.92994875

00:15:00.420 --> 00:15:01.460 low and and a low

NOTE Confidence: 0.92994875

00:15:01.460 --> 00:15:03.220 activity state in wakefulness, they

NOTE Confidence: 0.92994875

00:15:03.220 --> 00:15:04.520 switch on under ketamine.

NOTE Confidence: 0.9944453

00:15:05.060 --> 00:15:06.899 Cells that were previously highly

NOTE Confidence: 0.9944453

00:15:06.899 --> 00:15:08.740 active in wakefulness switch off,

NOTE Confidence: 0.9944453

00:15:08.740 --> 00:15:09.540 and this was true at

NOTE Confidence: 0.9944453

00:15:09.540 --> 00:15:10.760 these two different doses.

NOTE Confidence: 0.9675934

00:15:12.180 --> 00:15:13.695 And what what ketamine is

NOTE Confidence: 0.9675934

00:15:13.695 --> 00:15:15.535 doing is completely in contrast

NOTE Confidence: 0.9675934

00:15:15.535 --> 00:15:17.055 to other anesthetics that don't

NOTE Confidence: 0.9675934

00:15:17.055 --> 00:15:19.315 have disassociated properties. Here, cecoflurane

NOTE Confidence: 0.9571718

00:15:19.695 --> 00:15:21.155 at two percent, midazolam,

NOTE Confidence: 0.98178

00:15:22.415 --> 00:15:24.195 you could see that, neurons

NOTE Confidence: 0.98178

00:15:24.255 --> 00:15:26.175 active in wakefulness completely turn

NOTE Confidence: 0.98178

00:15:26.175 --> 00:15:27.600 off. You don't see this

NOTE Confidence: 0.98178

00:15:27.600 --> 00:15:28.160 sort of,

NOTE Confidence: 0.9177371

00:15:28.880 --> 00:15:30.820 reconfiguration of its cells activating

NOTE Confidence: 0.9177371

00:15:30.880 --> 00:15:31.940 under these states.

NOTE Confidence: 0.99392176

00:15:32.960 --> 00:15:34.000 And to see if this

NOTE Confidence: 0.99392176

00:15:34.000 --> 00:15:34.820 is a more,

NOTE Confidence: 0.98832124

00:15:35.440 --> 00:15:36.720 more of a global effect,

NOTE Confidence: 0.98832124

00:15:36.720 --> 00:15:38.080 I look I can look

NOTE Confidence: 0.98832124

00:15:38.080 --> 00:15:39.680 across the mouse's brain. Because

NOTE Confidence: 0.98832124

00:15:39.680 --> 00:15:41.120 the mouse's brain is quite

NOTE Confidence: 0.98832124

00:15:41.120 --> 00:15:42.945 flat, you can impose windows

NOTE Confidence: 0.98832124

00:15:42.945 --> 00:15:44.565 in different areas that are,

NOTE Confidence: 0.9783734

00:15:45.025 --> 00:15:46.404 related to different functions.

NOTE Confidence: 0.9914778

00:15:46.705 --> 00:15:48.305 And looking at secondary motor

NOTE Confidence: 0.9914778

00:15:48.305 --> 00:15:48.805 cortex,

NOTE Confidence: 0.9721635

00:15:50.545 --> 00:15:52.705 forelimb motor cortex, visual cortex,

NOTE Confidence: 0.9721635

00:15:52.705 --> 00:15:54.625 retrosplenial cortex, you find a

NOTE Confidence: 0.9721635

00:15:54.625 --> 00:15:56.485 very similar motif emerging.

NOTE Confidence: 0.9392404

00:15:57.380 --> 00:15:58.420 So this is not really

NOTE Confidence: 0.9392404

00:15:58.420 --> 00:16:00.260 specific to somatosensory but maybe

NOTE Confidence: 0.9392404

00:16:00.260 --> 00:16:01.000 more of

NOTE Confidence: 0.9183161

00:16:01.380 --> 00:16:01.960 a global,

NOTE Confidence: 0.9883031

00:16:02.420 --> 00:16:03.400 cortical feature.

NOTE Confidence: 0.9063925

00:16:03.940 --> 00:16:05.140 And in this work, and

NOTE Confidence: 0.9063925

00:16:05.140 --> 00:16:06.520 I I don't wanna,

NOTE Confidence: 0.9770595

00:16:06.980 --> 00:16:08.440 go into all the mechanisms,

NOTE Confidence: 0.9554659

00:16:09.540 --> 00:16:10.500 with you here today,

NOTE Confidence: 0.97193855

00:16:11.055 --> 00:16:12.015 because I wanna get to

NOTE Confidence: 0.97193855

00:16:12.015 --> 00:16:13.235 some of my newer work.

NOTE Confidence: 0.97193855

00:16:13.455 --> 00:16:15.635 But I really thoroughly entertained

NOTE Confidence: 0.99507564

00:16:16.255 --> 00:16:17.455 the fact that ketamine is

NOTE Confidence: 0.99507564

00:16:17.455 --> 00:16:18.495 a dirty drug, and it

NOTE Confidence: 0.99507564

00:16:18.495 --> 00:16:19.795 has effects on neuromodulation.

NOTE Confidence: 0.97176063

00:16:20.575 --> 00:16:21.855 It has circuit effects through

NOTE Confidence: 0.97176063

00:16:21.855 --> 00:16:23.075 GABAergic interneurons.

NOTE Confidence: 0.97069496

00:16:23.455 --> 00:16:25.215 It also has effects, through

NOTE Confidence: 0.97069496

00:16:25.215 --> 00:16:26.675 various different types of,

NOTE Confidence: 0.9748289

00:16:27.190 --> 00:16:28.570 channels, ion channels.

NOTE Confidence: 0.9756378

00:16:29.269 --> 00:16:30.730 And what this work,

NOTE Confidence: 0.95701456

00:16:31.829 --> 00:16:33.130 many experiments later,

NOTE Confidence: 0.9950364

00:16:34.630 --> 00:16:35.589 began to tell me is

NOTE Confidence: 0.9950364

00:16:35.589 --> 00:16:36.089 that

NOTE Confidence: 0.98049587

00:16:36.470 --> 00:16:37.990 you would need at least

NOTE Confidence: 0.98049587

00:16:37.990 --> 00:16:40.009 modulation of GABAergic interneurons,

NOTE Confidence: 0.9867731

00:16:40.485 --> 00:16:42.084 and you need suppression of

NOTE Confidence: 0.9867731

00:16:42.084 --> 00:16:44.404 HCN and NMDA channels to

NOTE Confidence: 0.9867731

00:16:44.404 --> 00:16:45.785 recreate this switch.

NOTE Confidence: 0.9618691

00:16:47.285 --> 00:16:47.785 And

NOTE Confidence: 0.9499098

00:16:48.325 --> 00:16:49.765 when I finished this work

NOTE Confidence: 0.9499098

00:16:49.765 --> 00:16:51.204 and I I noticed the

NOTE Confidence: 0.9499098

00:16:51.204 --> 00:16:52.565 switch that I think is

NOTE Confidence: 0.9499098

00:16:52.565 --> 00:16:54.630 arising in under a dissociative

NOTE Confidence: 0.95714396

00:16:55.010 --> 00:16:57.190 like state, I be began

NOTE Confidence: 0.95714396

00:16:57.250 --> 00:16:58.230 to think about,

NOTE Confidence: 0.986407

00:16:59.250 --> 00:17:00.870 how this might relate to,

NOTE Confidence: 0.986407

00:17:00.930 --> 00:17:02.770 like, the typical forms of

NOTE Confidence: 0.986407

00:17:02.770 --> 00:17:03.970 plasticity that a lot of

NOTE Confidence: 0.986407

00:17:03.970 --> 00:17:05.350 people describe and,

NOTE Confidence: 0.9663015

00:17:05.650 --> 00:17:07.010 folks like Alex Vaughn has

NOTE Confidence: 0.9663015

00:17:07.010 --> 00:17:08.505 described where you might see

NOTE Confidence: 0.9663015

00:17:08.505 --> 00:17:09.805 the birth of new connections.

NOTE Confidence: 0.9929247

00:17:10.345 --> 00:17:12.365 And I was, beginning to

NOTE Confidence: 0.994915

00:17:14.585 --> 00:17:15.705 oh, let let me let

NOTE Confidence: 0.994915

00:17:15.705 --> 00:17:16.744 me just take you on

NOTE Confidence: 0.994915

00:17:16.744 --> 00:17:17.725 this little sidetrack,

NOTE Confidence: 0.9924552

00:17:18.585 --> 00:17:20.025 to sort of connect that

NOTE Confidence: 0.9924552

00:17:20.025 --> 00:17:21.005 initial idea,

NOTE Confidence: 0.9860498

00:17:22.930 --> 00:17:24.230 with regards to disassociation

NOTE Confidence: 0.97620106

00:17:25.090 --> 00:17:26.630 to ketamine's antidepressant

NOTE Confidence: 0.95697105

00:17:27.010 --> 00:17:28.050 effect. And I I thought

NOTE Confidence: 0.95697105

00:17:28.050 --> 00:17:28.690 of a very, very,

NOTE Confidence: 0.96012104

00:17:30.609 --> 00:17:31.590 simple experiment,

NOTE Confidence: 0.99836373

00:17:32.130 --> 00:17:33.570 to get at this. And

NOTE Confidence: 0.99836373

00:17:33.570 --> 00:17:34.790 so in this experiment,

NOTE Confidence: 0.96883124

00:17:35.170 --> 00:17:36.070 I start with,

NOTE Confidence: 0.98388875

00:17:36.930 --> 00:17:38.965 naive mice, and I expose

NOTE Confidence: 0.98388875

00:17:38.965 --> 00:17:40.265 them to chronic stress.

NOTE Confidence: 0.9959551

00:17:40.725 --> 00:17:41.924 The prediction is is that

NOTE Confidence: 0.9959551

00:17:41.924 --> 00:17:43.605 you'll get a chronically stressed

NOTE Confidence: 0.9959551

00:17:43.605 --> 00:17:44.105 mouse.

NOTE Confidence: 0.9670966

00:17:45.205 --> 00:17:46.484 That mouse, if you expose

NOTE Confidence: 0.9670966

00:17:46.484 --> 00:17:47.605 it to ketamine at the

NOTE Confidence: 0.9670966

00:17:47.605 --> 00:17:48.904 subhypnotic dose,

NOTE Confidence: 0.9148787

00:17:49.845 --> 00:17:51.065 would, induce

NOTE Confidence: 0.9719174

00:17:52.010 --> 00:17:53.850 an antidepressant effect as measured

NOTE Confidence: 0.9719174

00:17:53.850 --> 00:17:55.770 by increase in immobility and

NOTE Confidence: 0.9719174

00:17:55.770 --> 00:17:56.510 tail suspension.

NOTE Confidence: 0.9123371

00:17:57.610 --> 00:17:58.730 But if you,

NOTE Confidence: 0.9672551

00:17:59.210 --> 00:18:00.510 then couple ketamine

NOTE Confidence: 0.8869262

00:18:00.810 --> 00:18:01.630 to isoflaurine,

NOTE Confidence: 0.9880609

00:18:02.730 --> 00:18:04.090 you might be able to

NOTE Confidence: 0.9880609

00:18:04.090 --> 00:18:04.590 quell,

NOTE Confidence: 0.9812735

00:18:05.130 --> 00:18:06.910 or suppress the dissociative

NOTE Confidence: 0.9483893

00:18:07.210 --> 00:18:09.445 effect and maybe render ketamine

NOTE Confidence: 0.9483893

00:18:09.585 --> 00:18:10.965 not useful to the mouse

NOTE Confidence: 0.9483893

00:18:11.265 --> 00:18:12.145 and you would,

NOTE Confidence: 0.96375966

00:18:12.865 --> 00:18:14.705 continue to show signs of

NOTE Confidence: 0.96375966

00:18:14.705 --> 00:18:16.085 a depression like state.

NOTE Confidence: 0.96980256

00:18:16.705 --> 00:18:17.445 And so,

NOTE Confidence: 0.94685555

00:18:18.865 --> 00:18:19.905 here you're looking at a

NOTE Confidence: 0.94685555

00:18:19.905 --> 00:18:20.725 very similar,

NOTE Confidence: 0.95287955

00:18:21.185 --> 00:18:22.385 experiment where a mouse is

NOTE Confidence: 0.95287955

00:18:22.385 --> 00:18:24.369 held in tail suspension and

NOTE Confidence: 0.95287955

00:18:24.429 --> 00:18:25.630 the mouse is exposed to

NOTE Confidence: 0.95287955

00:18:25.630 --> 00:18:26.669 this fifty mg per kg

NOTE Confidence: 0.95287955

00:18:26.669 --> 00:18:27.390 dose, and you could see

NOTE Confidence: 0.95287955

00:18:27.390 --> 00:18:28.429 that they failed to show

NOTE Confidence: 0.95287955

00:18:28.429 --> 00:18:30.109 that escape behavior and they

NOTE Confidence: 0.95287955

00:18:30.109 --> 00:18:31.970 have this sustained head twitch.

NOTE Confidence: 0.9461932

00:18:32.909 --> 00:18:34.109 When you couple ketamine with

NOTE Confidence: 0.9461932

00:18:34.109 --> 00:18:34.609 isoplaurine,

NOTE Confidence: 0.97674334

00:18:34.990 --> 00:18:36.529 you can completely eliminate,

NOTE Confidence: 0.9699535

00:18:37.565 --> 00:18:39.205 this vertical head twitch. It's

NOTE Confidence: 0.9699535

00:18:39.325 --> 00:18:40.685 again, I I I dare

NOTE Confidence: 0.9699535

00:18:40.685 --> 00:18:42.225 not to speculate what,

NOTE Confidence: 0.96702224

00:18:42.605 --> 00:18:44.225 the vertical head twitch means,

NOTE Confidence: 0.96702224

00:18:44.445 --> 00:18:45.805 but it is suggestive of

NOTE Confidence: 0.96702224

00:18:45.805 --> 00:18:46.865 perhaps maybe

NOTE Confidence: 0.7437738

00:18:47.165 --> 00:18:47.984 a psychedelic

NOTE Confidence: 0.8503941

00:18:48.285 --> 00:18:49.585 like response,

NOTE Confidence: 0.9358512

00:18:50.365 --> 00:18:50.765 but,

NOTE Confidence: 0.99965686

00:18:51.165 --> 00:18:52.065 hard to say.

NOTE Confidence: 0.98779976

00:18:52.440 --> 00:18:53.320 When you look at the

NOTE Confidence: 0.98779976

00:18:53.320 --> 00:18:54.139 neural activity,

NOTE Confidence: 0.99389505

00:18:55.399 --> 00:18:56.519 you could see that ketamine

NOTE Confidence: 0.99389505

00:18:56.519 --> 00:18:57.899 induces a reconfiguration

NOTE Confidence: 0.97155154

00:18:58.200 --> 00:18:59.639 of activity, but when you

NOTE Confidence: 0.97155154

00:18:59.639 --> 00:19:01.080 start to immediately couple that

NOTE Confidence: 0.97155154

00:19:01.080 --> 00:19:02.919 with isofluorine, the activity is

NOTE Confidence: 0.97155154

00:19:02.919 --> 00:19:03.419 lost.

NOTE Confidence: 0.9650592

00:19:04.359 --> 00:19:05.185 And that's true at a

NOTE Confidence: 0.9650592

00:19:05.185 --> 00:19:07.205 low moderate dose of isoflaurine

NOTE Confidence: 0.9650592

00:19:07.345 --> 00:19:08.305 or a higher dose of

NOTE Confidence: 0.9650592

00:19:08.305 --> 00:19:08.805 isoflaurine.

NOTE Confidence: 0.96396315

00:19:09.425 --> 00:19:10.305 And if you do the

NOTE Confidence: 0.96396315

00:19:10.305 --> 00:19:11.365 Converse experiment,

NOTE Confidence: 0.99690306

00:19:11.825 --> 00:19:13.765 we record activity under wakefulness

NOTE Confidence: 0.9214768

00:19:14.145 --> 00:19:15.045 followed by,

NOTE Confidence: 0.9526947

00:19:15.905 --> 00:19:16.405 isoflaurine.

NOTE Confidence: 0.97887343

00:19:17.740 --> 00:19:18.619 You could see the suppression

NOTE Confidence: 0.97887343

00:19:18.619 --> 00:19:19.679 of neural activity

NOTE Confidence: 0.8561046

00:19:19.980 --> 00:19:21.359 and followed by ketamine,

NOTE Confidence: 0.9983592

00:19:21.740 --> 00:19:23.039 you find that the activity

NOTE Confidence: 0.9983592

00:19:23.100 --> 00:19:24.380 is lost. So I think

NOTE Confidence: 0.9983592

00:19:24.380 --> 00:19:25.740 this is good evidence that

NOTE Confidence: 0.9983592

00:19:25.740 --> 00:19:27.100 when you couple the two,

NOTE Confidence: 0.9983592

00:19:27.100 --> 00:19:28.700 you start to eliminate or

NOTE Confidence: 0.9983592

00:19:28.700 --> 00:19:30.080 suppress neural activity.

NOTE Confidence: 0.9715983

00:19:31.179 --> 00:19:32.220 When you look at a

NOTE Confidence: 0.9715983

00:19:32.220 --> 00:19:32.720 more,

NOTE Confidence: 0.72529703

00:19:35.365 --> 00:19:35.865 classic,

NOTE Confidence: 0.84437406

00:19:39.125 --> 00:19:39.625 experiment

NOTE Confidence: 0.83984184

00:19:39.925 --> 00:19:40.244 that,

NOTE Confidence: 0.9782128

00:19:41.045 --> 00:19:42.325 would be indicative of a

NOTE Confidence: 0.9782128

00:19:42.325 --> 00:19:44.085 plasticity event such as CFOS

NOTE Confidence: 0.9782128

00:19:44.085 --> 00:19:44.585 expression,

NOTE Confidence: 0.97774804

00:19:46.060 --> 00:19:47.680 you find that ketamine induces

NOTE Confidence: 0.97774804

00:19:47.740 --> 00:19:49.440 CFOS expression in the prefrontal

NOTE Confidence: 0.97774804

00:19:49.580 --> 00:19:50.940 cortex. But when you couple

NOTE Confidence: 0.97774804

00:19:50.940 --> 00:19:51.440 this,

NOTE Confidence: 0.7432362

00:19:52.940 --> 00:19:53.680 with isoflaurine,

NOTE Confidence: 0.9989811

00:19:54.540 --> 00:19:56.640 the CFOS expression is reduced.

NOTE Confidence: 0.98743695

00:19:57.100 --> 00:19:58.140 And lastly, if you look

NOTE Confidence: 0.98743695

00:19:58.140 --> 00:19:58.800 at behavior

NOTE Confidence: 0.98534983

00:19:59.375 --> 00:20:01.234 where ketamine induces an antidepressant

NOTE Confidence: 0.98534983

00:20:01.375 --> 00:20:02.734 like effect, when you start

NOTE Confidence: 0.98534983

00:20:02.734 --> 00:20:04.355 to couple this with isoflurane,

NOTE Confidence: 0.9040757

00:20:05.215 --> 00:20:06.515 you fail to induce,

NOTE Confidence: 0.99962276

00:20:07.055 --> 00:20:07.875 an antidepressant

NOTE Confidence: 0.9971951

00:20:08.255 --> 00:20:08.755 effect.

NOTE Confidence: 0.9705569

00:20:09.135 --> 00:20:10.095 And I guess what that

NOTE Confidence: 0.9705569

00:20:10.095 --> 00:20:11.775 means, to me is that

NOTE Confidence: 0.9705569

00:20:11.775 --> 00:20:13.475 if you're gonna use ketamine,

NOTE Confidence: 0.9991846

00:20:14.510 --> 00:20:15.330 for the treatment

NOTE Confidence: 0.9747371

00:20:15.710 --> 00:20:17.410 of of, depression,

NOTE Confidence: 0.9902943

00:20:18.670 --> 00:20:20.430 you're gonna wanna probably give

NOTE Confidence: 0.9902943

00:20:20.430 --> 00:20:22.369 ketamine to an awake patient,

NOTE Confidence: 0.9727327

00:20:24.350 --> 00:20:25.570 that can experience,

NOTE Confidence: 0.97386414

00:20:26.350 --> 00:20:27.810 activity dependent plasticity,

NOTE Confidence: 0.9457118

00:20:29.015 --> 00:20:30.135 and and can,

NOTE Confidence: 0.99388474

00:20:30.695 --> 00:20:32.375 have complete benefit from from

NOTE Confidence: 0.99388474

00:20:32.375 --> 00:20:33.434 the drug exposure.

NOTE Confidence: 0.99846655

00:20:33.815 --> 00:20:34.774 I think if you begin

NOTE Confidence: 0.99846655

00:20:34.774 --> 00:20:35.914 to couple ketamine

NOTE Confidence: 0.9715125

00:20:36.375 --> 00:20:38.135 with, various different drugs that

NOTE Confidence: 0.9715125

00:20:38.135 --> 00:20:39.494 are sort of GABAergic in

NOTE Confidence: 0.9715125

00:20:39.494 --> 00:20:41.414 nature, you will begin to,

NOTE Confidence: 0.9715125

00:20:41.815 --> 00:20:43.590 suppress these, various forms of

NOTE Confidence: 0.9715125

00:20:43.590 --> 00:20:44.970 activity dependent plasticity.

NOTE Confidence: 0.9873935

00:20:45.750 --> 00:20:46.730 You'll and,

NOTE Confidence: 0.9535407

00:20:47.190 --> 00:20:47.850 and you'll,

NOTE Confidence: 0.7902732

00:20:49.830 --> 00:20:51.850 block the therapeutic effect.

NOTE Confidence: 0.96179867

00:20:56.365 --> 00:20:57.804 And, you might then also

NOTE Confidence: 0.96179867

00:20:57.804 --> 00:20:59.244 think in in the setting

NOTE Confidence: 0.96179867

00:20:59.244 --> 00:21:00.465 of ketamine with isoflaurine,

NOTE Confidence: 0.98497427

00:21:01.645 --> 00:21:03.005 you might not also be

NOTE Confidence: 0.98497427

00:21:03.005 --> 00:21:05.585 able to, trigger the disassociative

NOTE Confidence: 0.91392785

00:21:05.965 --> 00:21:07.484 state, but that's, again, hard

NOTE Confidence: 0.91392785

00:21:07.484 --> 00:21:09.105 to determine because the patient,

NOTE Confidence: 0.99993074

00:21:09.565 --> 00:21:10.304 is unconscious.

NOTE Confidence: 0.98381823

00:21:11.400 --> 00:21:12.600 And so in this first

NOTE Confidence: 0.98381823

00:21:12.600 --> 00:21:14.040 portion of the talk, I

NOTE Confidence: 0.98381823

00:21:14.040 --> 00:21:15.320 I really wanted to stress

NOTE Confidence: 0.98381823

00:21:15.320 --> 00:21:15.820 that,

NOTE Confidence: 0.95820886

00:21:16.840 --> 00:21:17.340 ketamine,

NOTE Confidence: 0.9589376

00:21:17.720 --> 00:21:18.760 can be modeled in a

NOTE Confidence: 0.9589376

00:21:18.760 --> 00:21:20.440 rodent and to induce a

NOTE Confidence: 0.9589376

00:21:20.440 --> 00:21:22.760 disassociated like state, and not

NOTE Confidence: 0.9589376

00:21:22.760 --> 00:21:24.280 one behavioral test will really

NOTE Confidence: 0.9589376

00:21:24.280 --> 00:21:25.480 capture that. But I think

NOTE Confidence: 0.9589376

00:21:25.480 --> 00:21:27.645 the the, summation of several

NOTE Confidence: 0.9589376

00:21:27.645 --> 00:21:28.945 different behavioral tests,

NOTE Confidence: 0.95837027

00:21:29.804 --> 00:21:31.904 can show that. Ketamine induces

NOTE Confidence: 0.95837027

00:21:31.965 --> 00:21:32.544 a behavioral,

NOTE Confidence: 0.9930193

00:21:33.085 --> 00:21:34.605 induces a rapid switch in

NOTE Confidence: 0.9930193

00:21:34.605 --> 00:21:35.345 neural activity

NOTE Confidence: 0.9544644

00:21:35.645 --> 00:21:37.025 and that this switch is

NOTE Confidence: 0.9544644

00:21:37.325 --> 00:21:38.945 widespread across the brain,

NOTE Confidence: 0.94371104

00:21:39.325 --> 00:21:40.410 and it seems that,

NOTE Confidence: 0.9976458

00:21:40.810 --> 00:21:41.310 ketamine,

NOTE Confidence: 0.9521754

00:21:42.250 --> 00:21:44.250 its antidepressant effects are sensitive

NOTE Confidence: 0.9521754

00:21:44.250 --> 00:21:46.170 to, general anesthetic. And I

NOTE Confidence: 0.9521754

00:21:46.170 --> 00:21:47.530 will touch again on this

NOTE Confidence: 0.9521754

00:21:47.530 --> 00:21:48.250 in a in a little

NOTE Confidence: 0.9521754

00:21:48.250 --> 00:21:49.470 bit later in the talk.

NOTE Confidence: 0.9995547

00:21:49.930 --> 00:21:50.430 So

NOTE Confidence: 0.9994537

00:21:51.050 --> 00:21:52.090 a few slides ago, I

NOTE Confidence: 0.9994537

00:21:52.090 --> 00:21:53.210 was sort of drawing in

NOTE Confidence: 0.9994537

00:21:53.210 --> 00:21:53.950 this concept

NOTE Confidence: 0.9948743

00:21:54.410 --> 00:21:54.910 that

NOTE Confidence: 0.99017125

00:21:55.234 --> 00:21:56.695 if you can induce disassociation,

NOTE Confidence: 0.9581366

00:21:57.234 --> 00:21:58.515 you can induce this rapid

NOTE Confidence: 0.9581366

00:21:58.515 --> 00:21:59.494 switch in activity,

NOTE Confidence: 0.98782116

00:22:00.035 --> 00:22:01.315 and then the prediction is

NOTE Confidence: 0.98782116

00:22:01.315 --> 00:22:01.895 is that,

NOTE Confidence: 0.99414647

00:22:02.915 --> 00:22:04.215 different forms of plasticity

NOTE Confidence: 0.9998033

00:22:04.915 --> 00:22:05.655 might be

NOTE Confidence: 0.99985677

00:22:05.955 --> 00:22:07.734 shown in cells that activate

NOTE Confidence: 0.9569164

00:22:08.869 --> 00:22:10.630 or cells conversely if they're

NOTE Confidence: 0.9569164

00:22:10.630 --> 00:22:11.130 suppressed.

NOTE Confidence: 0.987859

00:22:11.669 --> 00:22:13.350 And so I developed recently

NOTE Confidence: 0.987859

00:22:13.350 --> 00:22:15.109 a technique that enables you

NOTE Confidence: 0.987859

00:22:15.109 --> 00:22:16.149 to label cells in a

NOTE Confidence: 0.987859

00:22:16.149 --> 00:22:17.830 very sparse fashion, and you

NOTE Confidence: 0.987859

00:22:17.830 --> 00:22:19.289 can begin to record,

NOTE Confidence: 0.9723979

00:22:19.909 --> 00:22:21.269 not only the neural activity

NOTE Confidence: 0.9723979

00:22:21.269 --> 00:22:22.630 of that individual cell, but

NOTE Confidence: 0.9723979

00:22:22.630 --> 00:22:23.929 then you can also go

NOTE Confidence: 0.98499876

00:22:25.165 --> 00:22:27.165 more superficially or deeper into

NOTE Confidence: 0.98499876

00:22:27.165 --> 00:22:28.385 its dendritic regions,

NOTE Confidence: 0.98711234

00:22:29.085 --> 00:22:29.965 and you can look at

NOTE Confidence: 0.98711234

00:22:29.965 --> 00:22:31.645 the synapses and investigate how

NOTE Confidence: 0.98711234

00:22:31.645 --> 00:22:32.385 these synapses,

NOTE Confidence: 0.9606258

00:22:32.925 --> 00:22:34.525 acutely change with regards to

NOTE Confidence: 0.9606258

00:22:34.525 --> 00:22:35.665 preexisting synapses.

NOTE Confidence: 0.9829289

00:22:35.965 --> 00:22:37.005 But then, also, you can

NOTE Confidence: 0.9829289

00:22:37.005 --> 00:22:38.430 look at the formation of

NOTE Confidence: 0.9829289

00:22:38.590 --> 00:22:39.950 new synapses and see how

NOTE Confidence: 0.9829289

00:22:39.950 --> 00:22:40.770 that contributes

NOTE Confidence: 0.9132365

00:22:41.150 --> 00:22:42.670 to internal activity. And so

NOTE Confidence: 0.9132365

00:22:42.670 --> 00:22:43.790 in this example, you can

NOTE Confidence: 0.9132365

00:22:43.790 --> 00:22:44.770 see two cells

NOTE Confidence: 0.9379917

00:22:45.150 --> 00:22:46.290 very active in wakefulness

NOTE Confidence: 0.88512295

00:22:46.590 --> 00:22:48.510 following ketamine at this moderate

NOTE Confidence: 0.88512295

00:22:48.510 --> 00:22:50.369 dose. You could see its

NOTE Confidence: 0.88512295

00:22:50.590 --> 00:22:51.570 rapid suppression.

NOTE Confidence: 0.99754614

00:22:52.405 --> 00:22:52.905 And

NOTE Confidence: 0.96446896

00:22:53.765 --> 00:22:54.965 as I was doing these

NOTE Confidence: 0.96446896

00:22:54.965 --> 00:22:55.465 experiments,

NOTE Confidence: 0.99101734

00:22:56.325 --> 00:22:57.305 I was approached,

NOTE Confidence: 0.96096843

00:22:58.484 --> 00:23:00.325 by an old colleague that

NOTE Confidence: 0.96096843

00:23:00.325 --> 00:23:01.684 I met during my PhD

NOTE Confidence: 0.96096843

00:23:01.684 --> 00:23:02.645 and has been a close

NOTE Confidence: 0.96096843

00:23:02.645 --> 00:23:03.145 collaborator,

NOTE Confidence: 0.90146434

00:23:04.085 --> 00:23:04.530 and,

NOTE Confidence: 0.9005567

00:23:05.090 --> 00:23:06.369 he said, hey, Joe. Would

NOTE Confidence: 0.9005567

00:23:06.369 --> 00:23:07.810 you this is Lauren Luger

NOTE Confidence: 0.9005567

00:23:07.810 --> 00:23:09.330 at at UCSD now, but

NOTE Confidence: 0.9005567

00:23:09.330 --> 00:23:10.210 previously at,

NOTE Confidence: 0.8920279

00:23:11.410 --> 00:23:11.910 Janelia,

NOTE Confidence: 0.9862685

00:23:12.690 --> 00:23:13.970 said, hey, Joe. We've we've

NOTE Confidence: 0.9862685

00:23:13.970 --> 00:23:14.869 sort of reengineered

NOTE Confidence: 0.95765084

00:23:15.650 --> 00:23:17.910 a, ketamine sniffer a ketamine

NOTE Confidence: 0.95765084

00:23:17.970 --> 00:23:19.170 sensor, which they also call

NOTE Confidence: 0.95765084

00:23:19.170 --> 00:23:19.750 a sniffer.

NOTE Confidence: 0.95771617

00:23:20.195 --> 00:23:21.635 Would you be interested in

NOTE Confidence: 0.95771617

00:23:21.635 --> 00:23:22.915 sort of exploring this because

NOTE Confidence: 0.95771617

00:23:22.915 --> 00:23:24.215 of your interest in ketamine?

NOTE Confidence: 0.92372876

00:23:24.515 --> 00:23:25.415 I said absolutely.

NOTE Confidence: 0.96114624

00:23:26.835 --> 00:23:27.335 And,

NOTE Confidence: 0.9672023

00:23:28.035 --> 00:23:29.795 what this molecule is is

NOTE Confidence: 0.9672023

00:23:29.795 --> 00:23:31.984 is basically a a bacterial

NOTE Confidence: 0.94913465

00:23:33.000 --> 00:23:34.220 protein that has been,

NOTE Confidence: 0.964927

00:23:35.000 --> 00:23:37.260 exquisitely engineered to sense specifically

NOTE Confidence: 0.9701162

00:23:37.560 --> 00:23:39.080 ketamine. And in fact, in

NOTE Confidence: 0.9701162

00:23:39.080 --> 00:23:40.440 this new unpublished version of

NOTE Confidence: 0.9701162

00:23:40.440 --> 00:23:41.720 the sensor, we can actually

NOTE Confidence: 0.9701162

00:23:41.720 --> 00:23:42.780 begin to detect

NOTE Confidence: 0.98000735

00:23:43.320 --> 00:23:45.400 different enantiomers of ketamine in

NOTE Confidence: 0.98000735

00:23:45.400 --> 00:23:46.975 real time. And so if

NOTE Confidence: 0.98000735

00:23:46.975 --> 00:23:48.015 you're looking at this a

NOTE Confidence: 0.98000735

00:23:48.015 --> 00:23:49.054 panel, this is how the,

NOTE Confidence: 0.98000735

00:23:49.455 --> 00:23:50.515 sensor expresses,

NOTE Confidence: 0.9837008

00:23:50.895 --> 00:23:51.695 and what you can see

NOTE Confidence: 0.9837008

00:23:51.695 --> 00:23:53.135 here, this is fluorescence over

NOTE Confidence: 0.9837008

00:23:53.135 --> 00:23:55.054 time. And following ketamine injection,

NOTE Confidence: 0.9837008

00:23:55.054 --> 00:23:56.914 you could see within almost

NOTE Confidence: 0.9837008

00:23:57.054 --> 00:23:58.975 ten seconds, ketamine is already

NOTE Confidence: 0.9837008

00:23:58.975 --> 00:24:00.414 entering the brain, meaning it's

NOTE Confidence: 0.9837008

00:24:00.414 --> 00:24:02.190 circulating from the intraperitoneal

NOTE Confidence: 0.99629956

00:24:02.890 --> 00:24:03.390 cavity

NOTE Confidence: 0.9706

00:24:03.770 --> 00:24:05.770 into the circulatory system, getting

NOTE Confidence: 0.9706

00:24:05.770 --> 00:24:06.810 into the brain through the

NOTE Confidence: 0.9706

00:24:06.810 --> 00:24:08.330 blood brain barrier, and being

NOTE Confidence: 0.9706

00:24:08.330 --> 00:24:09.550 detected locally,

NOTE Confidence: 0.95886546

00:24:10.410 --> 00:24:11.930 in in various different brain

NOTE Confidence: 0.95886546

00:24:11.930 --> 00:24:12.890 regions within,

NOTE Confidence: 0.96694267

00:24:13.850 --> 00:24:15.150 basically, a ten second

NOTE Confidence: 0.86699253

00:24:15.530 --> 00:24:16.430 period of time.

NOTE Confidence: 0.97830176

00:24:17.405 --> 00:24:18.765 And, interestingly, if you look

NOTE Confidence: 0.97830176

00:24:18.765 --> 00:24:20.125 at some of these kinetic

NOTE Confidence: 0.97830176

00:24:20.125 --> 00:24:20.625 measurements,

NOTE Confidence: 0.96173054

00:24:21.005 --> 00:24:22.605 you find that, the time

NOTE Confidence: 0.96173054

00:24:22.605 --> 00:24:23.005 to,

NOTE Confidence: 0.9962423

00:24:23.725 --> 00:24:25.325 peak signal of ketamine is

NOTE Confidence: 0.9962423

00:24:25.325 --> 00:24:27.025 around ten to fifteen minutes,

NOTE Confidence: 0.9962423

00:24:27.244 --> 00:24:28.705 until it gets to its

NOTE Confidence: 0.9712795

00:24:29.325 --> 00:24:30.145 final fluorescence,

NOTE Confidence: 0.96268535

00:24:30.929 --> 00:24:32.950 its max, fluorescence intensity.

NOTE Confidence: 0.98016965

00:24:33.490 --> 00:24:35.169 And that's interesting, but you

NOTE Confidence: 0.98016965

00:24:35.169 --> 00:24:36.529 said you might say, Joel,

NOTE Confidence: 0.98016965

00:24:36.529 --> 00:24:37.889 I can probably measure that

NOTE Confidence: 0.98016965

00:24:37.889 --> 00:24:38.929 in blood, and you wouldn't

NOTE Confidence: 0.98016965

00:24:38.929 --> 00:24:40.129 be wrong. What I think

NOTE Confidence: 0.98016965

00:24:40.129 --> 00:24:41.409 is interesting about some of

NOTE Confidence: 0.98016965

00:24:41.409 --> 00:24:43.169 this unpublished data is that

NOTE Confidence: 0.98016965

00:24:43.169 --> 00:24:44.369 you can begin to use

NOTE Confidence: 0.98016965

00:24:44.369 --> 00:24:46.049 clever genetic tricks to target

NOTE Confidence: 0.98016965

00:24:46.049 --> 00:24:47.675 these sensors to various different

NOTE Confidence: 0.98016965

00:24:47.675 --> 00:24:49.355 locations within a neuron. You

NOTE Confidence: 0.98016965

00:24:49.355 --> 00:24:50.415 could target this,

NOTE Confidence: 0.78137755

00:24:51.435 --> 00:24:53.135 sensor specifically the cytoplasm

NOTE Confidence: 0.9981062

00:24:53.435 --> 00:24:54.494 versus the nucleus

NOTE Confidence: 0.93359345

00:24:55.115 --> 00:24:56.494 and plasma membrane.

NOTE Confidence: 0.97904164

00:24:57.035 --> 00:24:58.075 And what I'm showing you

NOTE Confidence: 0.97904164

00:24:58.075 --> 00:24:59.115 here is sort of how

NOTE Confidence: 0.97904164

00:24:59.115 --> 00:25:00.335 these sensors express,

NOTE Confidence: 0.96195513

00:25:01.140 --> 00:25:02.180 And here on the right

NOTE Confidence: 0.96195513

00:25:02.180 --> 00:25:03.300 looking at these traces is

NOTE Confidence: 0.96195513

00:25:03.300 --> 00:25:04.359 what you find

NOTE Confidence: 0.9968536

00:25:04.740 --> 00:25:06.200 is something really amazing.

NOTE Confidence: 0.95226425

00:25:06.660 --> 00:25:08.020 When you sense ketamine at

NOTE Confidence: 0.95226425

00:25:08.020 --> 00:25:10.180 the plasma membrane, it's rapid

NOTE Confidence: 0.95226425

00:25:10.180 --> 00:25:11.859 in its detection, and it's

NOTE Confidence: 0.95226425

00:25:11.859 --> 00:25:13.300 relatively short lived, and this

NOTE Confidence: 0.95226425

00:25:13.300 --> 00:25:14.980 sort of mirrors plasma men

NOTE Confidence: 0.95226425

00:25:15.220 --> 00:25:15.720 plasma

NOTE Confidence: 0.9971308

00:25:16.215 --> 00:25:17.355 measurements of ketamine.

NOTE Confidence: 0.98984796

00:25:18.054 --> 00:25:19.494 When you look within the

NOTE Confidence: 0.98984796

00:25:19.494 --> 00:25:21.015 cell, what you begin to

NOTE Confidence: 0.98984796

00:25:21.015 --> 00:25:21.895 find is that there's a

NOTE Confidence: 0.98984796

00:25:21.895 --> 00:25:23.494 rapid detection within ketamine. So

NOTE Confidence: 0.98984796

00:25:23.494 --> 00:25:25.015 ketamine is just going right

NOTE Confidence: 0.98984796

00:25:25.015 --> 00:25:26.934 through the plasma membrane, getting

NOTE Confidence: 0.98984796

00:25:26.934 --> 00:25:27.914 into the cytoplasm,

NOTE Confidence: 0.9930406

00:25:28.215 --> 00:25:29.494 and even getting into the

NOTE Confidence: 0.9930406

00:25:29.494 --> 00:25:29.994 nucleus.

NOTE Confidence: 0.9949873

00:25:30.960 --> 00:25:33.039 And what's outstanding is the

NOTE Confidence: 0.9949873

00:25:33.039 --> 00:25:34.320 fact that this,

NOTE Confidence: 0.9996679

00:25:34.720 --> 00:25:35.220 recording

NOTE Confidence: 0.9105602

00:25:35.520 --> 00:25:36.880 signals that in this particular

NOTE Confidence: 0.9105602

00:25:36.880 --> 00:25:37.919 mouse given a ten mg

NOTE Confidence: 0.9105602

00:25:37.919 --> 00:25:39.600 per kg injection, which is

NOTE Confidence: 0.9105602

00:25:39.600 --> 00:25:41.039 the common injection to induce

NOTE Confidence: 0.9105602

00:25:41.039 --> 00:25:42.640 an antidepressant like effect of

NOTE Confidence: 0.9105602

00:25:42.640 --> 00:25:43.220 a mouse,

NOTE Confidence: 0.9663814

00:25:44.165 --> 00:25:45.924 these signals are sustained for

NOTE Confidence: 0.9663814

00:25:45.924 --> 00:25:46.665 over hours.

NOTE Confidence: 0.9829679

00:25:47.525 --> 00:25:48.325 And if you look at

NOTE Confidence: 0.9829679

00:25:48.325 --> 00:25:49.845 ninety minutes, you see sustained

NOTE Confidence: 0.9829679

00:25:49.845 --> 00:25:50.345 signal.

NOTE Confidence: 0.99858534

00:25:51.044 --> 00:25:51.544 So

NOTE Confidence: 0.9656567

00:25:51.924 --> 00:25:53.525 the classic sort of description

NOTE Confidence: 0.9656567

00:25:53.525 --> 00:25:55.205 of ketamine interacting with the

NOTE Confidence: 0.9656567

00:25:55.205 --> 00:25:56.905 receptor at the plasma membrane

NOTE Confidence: 0.9679185

00:25:57.440 --> 00:25:59.460 is is is rather superficial,

NOTE Confidence: 0.9713064

00:26:00.080 --> 00:26:02.559 and, ketamine is completely permeating

NOTE Confidence: 0.9713064

00:26:02.559 --> 00:26:03.920 a neuron from its,

NOTE Confidence: 0.9991394

00:26:04.559 --> 00:26:05.619 receptor surfaces

NOTE Confidence: 0.94958436

00:26:06.080 --> 00:26:07.280 to all the way the

NOTE Confidence: 0.94958436

00:26:07.280 --> 00:26:09.619 the the within the nucleus.

NOTE Confidence: 0.8950272

00:26:10.665 --> 00:26:12.125 And we don't quite understand

NOTE Confidence: 0.8950272

00:26:12.345 --> 00:26:12.505 the,

NOTE Confidence: 0.90614724

00:26:14.185 --> 00:26:14.685 implications

NOTE Confidence: 0.95631105

00:26:15.065 --> 00:26:17.005 of these sort of, observations.

NOTE Confidence: 0.9623378

00:26:19.065 --> 00:26:20.265 And so you could see

NOTE Confidence: 0.9623378

00:26:20.265 --> 00:26:21.645 I easily get sidetracked,

NOTE Confidence: 0.98048997

00:26:22.800 --> 00:26:24.240 and which which brings me

NOTE Confidence: 0.98048997

00:26:24.240 --> 00:26:26.020 to this, question of nitrous

NOTE Confidence: 0.98048997

00:26:26.080 --> 00:26:28.020 oxide. And when I was

NOTE Confidence: 0.98048997

00:26:28.240 --> 00:26:29.460 doing this very,

NOTE Confidence: 0.97290826

00:26:31.600 --> 00:26:33.120 very experiment, I was approached

NOTE Confidence: 0.97290826

00:26:33.120 --> 00:26:34.080 by a colleague in the

NOTE Confidence: 0.97290826

00:26:34.080 --> 00:26:35.680 field of anesthesia named Peter

NOTE Confidence: 0.97290826

00:26:35.680 --> 00:26:36.800 Nagley, who,

NOTE Confidence: 0.97800887

00:26:37.744 --> 00:26:39.265 is working at the University

NOTE Confidence: 0.97800887

00:26:39.265 --> 00:26:41.025 of Chicago, and he was

NOTE Confidence: 0.97800887

00:26:41.025 --> 00:26:41.525 basically,

NOTE Confidence: 0.9913467

00:26:42.705 --> 00:26:44.385 thinking about nitrous oxide and

NOTE Confidence: 0.9913467

00:26:44.385 --> 00:26:45.365 its role in

NOTE Confidence: 0.7628581

00:26:45.825 --> 00:26:47.205 in in the treatment of

NOTE Confidence: 0.7628581

00:26:47.345 --> 00:26:47.905 resistant to

NOTE Confidence: 0.82753533

00:26:48.785 --> 00:26:50.165 treatment resistant depression.

NOTE Confidence: 0.98995167

00:26:50.630 --> 00:26:51.510 And he said, Joe, you

NOTE Confidence: 0.98995167

00:26:51.510 --> 00:26:52.310 know, it's great that you're

NOTE Confidence: 0.98995167

00:26:52.310 --> 00:26:53.290 working with ketamine,

NOTE Confidence: 0.99068576

00:26:54.070 --> 00:26:54.810 but ketamine,

NOTE Confidence: 0.96089554

00:26:55.430 --> 00:26:56.070 as you know, is a

NOTE Confidence: 0.96089554

00:26:56.070 --> 00:26:57.290 dirty drug. And,

NOTE Confidence: 0.9811286

00:26:57.910 --> 00:26:59.670 you know, moreover, you know,

NOTE Confidence: 0.9811286

00:26:59.670 --> 00:27:00.790 ketamine has a lot of

NOTE Confidence: 0.9811286

00:27:00.790 --> 00:27:01.910 metabolites that are thought to

NOTE Confidence: 0.9811286

00:27:01.910 --> 00:27:03.110 be neuroactive. They could be

NOTE Confidence: 0.9811286

00:27:03.110 --> 00:27:04.630 dissociative. They could also be

NOTE Confidence: 0.9811286

00:27:04.630 --> 00:27:05.130 antidepressant.

NOTE Confidence: 0.9470623

00:27:06.485 --> 00:27:07.845 And you really don't know,

NOTE Confidence: 0.95824504

00:27:08.325 --> 00:27:09.525 how that's all gonna shake

NOTE Confidence: 0.95824504

00:27:09.525 --> 00:27:10.025 out,

NOTE Confidence: 0.99539137

00:27:10.485 --> 00:27:11.765 so why not work with

NOTE Confidence: 0.99539137

00:27:11.765 --> 00:27:12.885 a cleaner drug? And I

NOTE Confidence: 0.99539137

00:27:12.885 --> 00:27:14.165 said, well, that's, you know,

NOTE Confidence: 0.99539137

00:27:14.165 --> 00:27:14.985 an interesting,

NOTE Confidence: 0.97970945

00:27:15.845 --> 00:27:16.825 you know, observation.

NOTE Confidence: 0.9896484

00:27:17.525 --> 00:27:18.025 And

NOTE Confidence: 0.9714637

00:27:19.429 --> 00:27:20.390 and he's like, well, let

NOTE Confidence: 0.9714637

00:27:20.390 --> 00:27:21.350 me just show I'll show

NOTE Confidence: 0.9714637

00:27:21.350 --> 00:27:22.549 you my data, and,

NOTE Confidence: 0.9944833

00:27:23.270 --> 00:27:24.710 I can maybe convince you

NOTE Confidence: 0.9944833

00:27:24.710 --> 00:27:26.230 to to explore this in

NOTE Confidence: 0.9944833

00:27:26.230 --> 00:27:27.450 in your preclinical

NOTE Confidence: 0.9939836

00:27:27.830 --> 00:27:28.330 models.

NOTE Confidence: 0.9631185

00:27:29.030 --> 00:27:29.510 And,

NOTE Confidence: 0.9675436

00:27:30.309 --> 00:27:31.669 so so so he did.

NOTE Confidence: 0.9675436

00:27:31.669 --> 00:27:31.990 And,

NOTE Confidence: 0.9530683

00:27:32.804 --> 00:27:34.085 long story short, he convinced

NOTE Confidence: 0.9530683

00:27:34.085 --> 00:27:35.205 me this was worthy of

NOTE Confidence: 0.9530683

00:27:35.205 --> 00:27:35.705 pursuit.

NOTE Confidence: 0.9939722

00:27:36.565 --> 00:27:37.524 And one thing that I

NOTE Confidence: 0.9939722

00:27:37.524 --> 00:27:38.725 thought was really interesting is

NOTE Confidence: 0.9939722

00:27:38.725 --> 00:27:39.684 that, you know, when you

NOTE Confidence: 0.9939722

00:27:39.684 --> 00:27:40.725 look back at some of

NOTE Confidence: 0.9939722

00:27:40.725 --> 00:27:41.304 the older,

NOTE Confidence: 0.99799937

00:27:41.684 --> 00:27:43.044 in vitro data with regards

NOTE Confidence: 0.99799937

00:27:43.044 --> 00:27:45.065 to nitrous oxide molecular mechanisms,

NOTE Confidence: 0.92522216

00:27:45.684 --> 00:27:47.205 nitrous oxide is again thought

NOTE Confidence: 0.92522216

00:27:47.205 --> 00:27:49.169 to be primarily an NMDA

NOTE Confidence: 0.92522216

00:27:49.169 --> 00:27:49.669 antagonist,

NOTE Confidence: 0.9898814

00:27:50.210 --> 00:27:51.490 but that was really never

NOTE Confidence: 0.9898814

00:27:51.490 --> 00:27:53.169 tested in the mammalian brain.

NOTE Confidence: 0.9898814

00:27:53.169 --> 00:27:54.130 It was all done in

NOTE Confidence: 0.9898814

00:27:54.130 --> 00:27:54.850 sort of,

NOTE Confidence: 0.7004827

00:27:55.330 --> 00:27:56.309 altered neurons

NOTE Confidence: 0.9685849

00:27:56.929 --> 00:27:58.070 or or brain slice.

NOTE Confidence: 0.9838382

00:27:58.690 --> 00:28:00.290 And what really got me

NOTE Confidence: 0.9838382

00:28:00.290 --> 00:28:01.785 hooked and really engaged in

NOTE Confidence: 0.9838382

00:28:01.785 --> 00:28:03.625 in this particular study is

NOTE Confidence: 0.9838382

00:28:03.625 --> 00:28:05.225 the fact that nitrous oxide

NOTE Confidence: 0.9838382

00:28:05.225 --> 00:28:06.585 is a gas. It's only,

NOTE Confidence: 0.90893316

00:28:07.465 --> 00:28:08.205 three atoms.

NOTE Confidence: 0.96093047

00:28:11.785 --> 00:28:13.625 And, nitrous oxide has to

NOTE Confidence: 0.96093047

00:28:13.625 --> 00:28:14.285 be inhaled.

NOTE Confidence: 0.88070995

00:28:15.065 --> 00:28:16.265 It so it it,

NOTE Confidence: 0.9492855

00:28:17.090 --> 00:28:18.290 it will be inhaled, and

NOTE Confidence: 0.9492855

00:28:18.290 --> 00:28:20.429 it'll, this gas will,

NOTE Confidence: 0.98135257

00:28:21.010 --> 00:28:22.290 partition into the blood and

NOTE Confidence: 0.98135257

00:28:22.290 --> 00:28:23.170 then get to the brain

NOTE Confidence: 0.98135257

00:28:23.170 --> 00:28:24.609 and diffuse across the blood

NOTE Confidence: 0.98135257

00:28:24.609 --> 00:28:25.890 brain barrier and then,

NOTE Confidence: 0.9820158

00:28:26.690 --> 00:28:27.890 you know, interact and do

NOTE Confidence: 0.9820158

00:28:27.890 --> 00:28:29.170 its thing, and then it

NOTE Confidence: 0.9820158

00:28:29.170 --> 00:28:30.315 has to be blown off.

NOTE Confidence: 0.9585422

00:28:30.715 --> 00:28:32.634 And what's even more surprising

NOTE Confidence: 0.9585422

00:28:32.634 --> 00:28:33.855 is that there is no

NOTE Confidence: 0.86614835

00:28:34.234 --> 00:28:35.914 metabolite of nitrous oxide. It

NOTE Confidence: 0.86614835

00:28:35.914 --> 00:28:37.274 is breathed in as nitrous

NOTE Confidence: 0.86614835

00:28:37.274 --> 00:28:38.315 oxide. It is inhaled as

NOTE Confidence: 0.86614835

00:28:38.315 --> 00:28:38.815 nitrous

NOTE Confidence: 0.97757983

00:28:39.115 --> 00:28:40.875 oxide. So if anything, I

NOTE Confidence: 0.97757983

00:28:40.875 --> 00:28:42.235 uncover with regards to a

NOTE Confidence: 0.97757983

00:28:42.235 --> 00:28:42.735 mechanism

NOTE Confidence: 0.9876174

00:28:43.320 --> 00:28:44.919 has to be related to

NOTE Confidence: 0.9876174

00:28:44.919 --> 00:28:46.460 the drug exposure itself.

NOTE Confidence: 0.9674293

00:28:48.440 --> 00:28:49.559 And so, you know, this

NOTE Confidence: 0.9674293

00:28:49.559 --> 00:28:50.679 is one example that he

NOTE Confidence: 0.9674293

00:28:50.679 --> 00:28:51.720 showed me of a patient

NOTE Confidence: 0.9674293

00:28:51.720 --> 00:28:53.500 who is treatment resistant depressed,

NOTE Confidence: 0.9751423

00:28:54.600 --> 00:28:55.559 who who came in for

NOTE Confidence: 0.9751423

00:28:55.559 --> 00:28:56.299 their trial,

NOTE Confidence: 0.9659326

00:28:56.625 --> 00:28:58.305 received one hour duration of

NOTE Confidence: 0.9659326

00:28:58.305 --> 00:28:59.825 fifty percent nitrous oxide. So

NOTE Confidence: 0.9659326

00:28:59.825 --> 00:29:01.105 this is not an anesthetic

NOTE Confidence: 0.9659326

00:29:01.105 --> 00:29:02.385 dose of nitrous oxide. This

NOTE Confidence: 0.9659326

00:29:02.385 --> 00:29:03.265 is something that you would

NOTE Confidence: 0.9659326

00:29:03.265 --> 00:29:04.945 get in a dentist's office

NOTE Confidence: 0.9659326

00:29:04.945 --> 00:29:05.765 if you're getting,

NOTE Confidence: 0.9982074

00:29:06.465 --> 00:29:07.845 your wisdom teeth pulled.

NOTE Confidence: 0.96098155

00:29:08.385 --> 00:29:09.265 You could see that there's

NOTE Confidence: 0.96098155

00:29:09.265 --> 00:29:10.385 a rapid reduction in the

NOTE Confidence: 0.96098155

00:29:10.385 --> 00:29:10.885 symptoms.

NOTE Confidence: 0.98075366

00:29:11.730 --> 00:29:12.550 This patient,

NOTE Confidence: 0.76307315

00:29:14.370 --> 00:29:15.430 eventually was,

NOTE Confidence: 0.9921712

00:29:16.050 --> 00:29:17.430 crossed over to the placebo

NOTE Confidence: 0.9921712

00:29:17.490 --> 00:29:18.390 group in February

NOTE Confidence: 0.92313385

00:29:18.930 --> 00:29:20.290 and then in March had

NOTE Confidence: 0.92313385

00:29:20.290 --> 00:29:21.730 some a worsening of symptoms

NOTE Confidence: 0.92313385

00:29:21.730 --> 00:29:23.330 and then subsequently received a

NOTE Confidence: 0.92313385

00:29:23.330 --> 00:29:24.310 twenty five percent,

NOTE Confidence: 0.9596783

00:29:26.075 --> 00:29:28.315 inhalation of nitrous oxide, and

NOTE Confidence: 0.9596783

00:29:28.315 --> 00:29:29.055 their symptoms

NOTE Confidence: 0.9688608

00:29:29.435 --> 00:29:31.295 were, further improved.

NOTE Confidence: 0.996133

00:29:32.235 --> 00:29:33.855 And so in this study,

NOTE Confidence: 0.9995166

00:29:34.395 --> 00:29:35.215 I transitioned

NOTE Confidence: 0.945078

00:29:35.675 --> 00:29:37.835 to studying three cohorts of

NOTE Confidence: 0.945078

00:29:37.835 --> 00:29:39.755 mice, a control group, and

NOTE Confidence: 0.945078

00:29:39.755 --> 00:29:41.295 two chronic stress groups,

NOTE Confidence: 0.99976975

00:29:41.740 --> 00:29:42.240 one

NOTE Confidence: 0.93626165

00:29:42.860 --> 00:29:43.360 which,

NOTE Confidence: 0.99301094

00:29:43.740 --> 00:29:44.240 receives

NOTE Confidence: 0.8661098

00:29:44.779 --> 00:29:46.240 chronic social defeat,

NOTE Confidence: 0.98213446

00:29:46.860 --> 00:29:48.299 by an aggressor mouse, and

NOTE Confidence: 0.98213446

00:29:48.299 --> 00:29:49.600 that lasts for ten days.

NOTE Confidence: 0.98213446

00:29:49.659 --> 00:29:50.539 And the other is a

NOTE Confidence: 0.98213446

00:29:50.539 --> 00:29:51.899 more classic model where you

NOTE Confidence: 0.98213446

00:29:51.899 --> 00:29:52.880 infuse choristerone

NOTE Confidence: 0.9512416

00:29:53.419 --> 00:29:54.539 and the drinking order for

NOTE Confidence: 0.9512416

00:29:54.539 --> 00:29:55.820 twenty one days, and that

NOTE Confidence: 0.9512416

00:29:55.820 --> 00:29:56.640 is a pharmacological

NOTE Confidence: 0.9997996

00:29:57.615 --> 00:29:58.355 way to

NOTE Confidence: 0.85374755

00:29:58.655 --> 00:30:00.755 induce a depression like state,

NOTE Confidence: 0.9291074

00:30:01.455 --> 00:30:02.975 if I may. And then

NOTE Confidence: 0.9291074

00:30:02.975 --> 00:30:04.175 so these mice are gonna

NOTE Confidence: 0.9291074

00:30:04.175 --> 00:30:05.695 be chronically stressed, and then

NOTE Confidence: 0.9291074

00:30:05.695 --> 00:30:06.995 in and then,

NOTE Confidence: 0.8993761

00:30:08.895 --> 00:30:10.915 following that will be, imaged

NOTE Confidence: 0.8993761

00:30:11.215 --> 00:30:12.755 under the two photon microscope.

NOTE Confidence: 0.9933981

00:30:13.279 --> 00:30:14.960 And so, I devised a

NOTE Confidence: 0.9933981

00:30:14.960 --> 00:30:16.260 way to mix,

NOTE Confidence: 0.98347795

00:30:16.639 --> 00:30:18.399 nitrous oxide, and that's with

NOTE Confidence: 0.98347795

00:30:18.399 --> 00:30:19.519 oxygen and and,

NOTE Confidence: 0.9684268

00:30:20.399 --> 00:30:21.840 a hundred percent nitrous oxide

NOTE Confidence: 0.9684268

00:30:21.840 --> 00:30:23.120 through a blender. And I

NOTE Confidence: 0.9684268

00:30:23.120 --> 00:30:24.500 can create a fifty percent

NOTE Confidence: 0.9870667

00:30:25.865 --> 00:30:27.465 concentration. And I can monitor

NOTE Confidence: 0.9870667

00:30:27.465 --> 00:30:29.305 also how that, is being

NOTE Confidence: 0.9870667

00:30:29.305 --> 00:30:30.345 delivered to a mouse by

NOTE Confidence: 0.9870667

00:30:30.345 --> 00:30:31.865 using a gas analyzer, something

NOTE Confidence: 0.9870667

00:30:31.865 --> 00:30:33.065 that we commonly use in

NOTE Confidence: 0.9870667

00:30:33.065 --> 00:30:34.125 the operating room,

NOTE Confidence: 0.90045387

00:30:34.745 --> 00:30:36.265 and then the remaining gas

NOTE Confidence: 0.90045387

00:30:36.265 --> 00:30:36.665 is,

NOTE Confidence: 0.9904472

00:30:37.065 --> 00:30:37.565 scavenged.

NOTE Confidence: 0.97732604

00:30:38.640 --> 00:30:39.040 And,

NOTE Confidence: 0.87632805

00:30:39.440 --> 00:30:40.080 in this,

NOTE Confidence: 0.92019385

00:30:40.560 --> 00:30:42.720 experiment, I record across a

NOTE Confidence: 0.92019385

00:30:42.720 --> 00:30:44.080 prefrontal area called c g

NOTE Confidence: 0.92019385

00:30:44.080 --> 00:30:45.200 one, which will be equivalent

NOTE Confidence: 0.92019385

00:30:45.200 --> 00:30:46.880 to the anterior cingulate cortex

NOTE Confidence: 0.92019385

00:30:46.880 --> 00:30:47.620 in the human.

NOTE Confidence: 0.9994097

00:30:48.400 --> 00:30:49.540 And we can image

NOTE Confidence: 0.99087214

00:30:49.855 --> 00:30:51.375 basically across this cortical,

NOTE Confidence: 0.96853185

00:30:51.695 --> 00:30:53.134 across this cortical column through

NOTE Confidence: 0.96853185

00:30:53.134 --> 00:30:54.174 layer two, three, and layer

NOTE Confidence: 0.96853185

00:30:54.174 --> 00:30:54.674 five.

NOTE Confidence: 0.9953743

00:30:57.934 --> 00:30:58.975 Before I show you some

NOTE Confidence: 0.9953743

00:30:58.975 --> 00:31:00.495 of the imaging data, I

NOTE Confidence: 0.9953743

00:31:00.495 --> 00:31:01.774 just wanna convince you that

NOTE Confidence: 0.9953743

00:31:01.774 --> 00:31:03.634 we can detect, an antidepressant

NOTE Confidence: 0.9988259

00:31:04.014 --> 00:31:04.755 like effect

NOTE Confidence: 0.9539564

00:31:05.160 --> 00:31:06.840 following nitrous oxide in the

NOTE Confidence: 0.9539564

00:31:06.840 --> 00:31:08.200 chronic stress group. So here

NOTE Confidence: 0.9539564

00:31:08.200 --> 00:31:08.860 you're looking

NOTE Confidence: 0.8961652

00:31:09.240 --> 00:31:11.080 at, immobility time and tail

NOTE Confidence: 0.8961652

00:31:11.080 --> 00:31:12.860 suspension. Here you're looking at

NOTE Confidence: 0.8655497

00:31:16.520 --> 00:31:18.280 open arm time and elevated

NOTE Confidence: 0.8655497

00:31:18.280 --> 00:31:19.900 plus assess whether a mouse

NOTE Confidence: 0.9660705

00:31:20.505 --> 00:31:22.265 displays a depression like state.

NOTE Confidence: 0.9660705

00:31:22.265 --> 00:31:23.385 It's not like one test.

NOTE Confidence: 0.9660705

00:31:23.385 --> 00:31:25.005 It's a combination of tests,

NOTE Confidence: 0.9660705

00:31:25.065 --> 00:31:26.445 but you can see that

NOTE Confidence: 0.94030356

00:31:27.225 --> 00:31:28.745 that the oxygen group, which

NOTE Confidence: 0.94030356

00:31:28.745 --> 00:31:29.485 is in green,

NOTE Confidence: 0.978287

00:31:29.785 --> 00:31:31.945 begins to separate from, the

NOTE Confidence: 0.978287

00:31:31.945 --> 00:31:33.065 blue group, which is nitrous

NOTE Confidence: 0.978287

00:31:33.065 --> 00:31:34.445 oxide following treatment.

NOTE Confidence: 0.9951195

00:31:34.830 --> 00:31:36.750 And so there's, some behavioral

NOTE Confidence: 0.9951195

00:31:36.750 --> 00:31:38.289 evidence that nitrous oxide

NOTE Confidence: 0.9793215

00:31:38.590 --> 00:31:40.289 induces a behavioral change.

NOTE Confidence: 0.9807813

00:31:40.990 --> 00:31:42.590 And my hypothesis leading into

NOTE Confidence: 0.9807813

00:31:42.590 --> 00:31:45.010 this experiment, unfortunately, wasn't too

NOTE Confidence: 0.9807813

00:31:45.230 --> 00:31:46.669 thoughtful or creative. I thought

NOTE Confidence: 0.9807813

00:31:46.669 --> 00:31:47.650 there might be,

NOTE Confidence: 0.96172726

00:31:49.375 --> 00:31:50.674 sort of a reconfiguration

NOTE Confidence: 0.92746985

00:31:51.135 --> 00:31:52.174 like I saw with ketamine

NOTE Confidence: 0.92746985

00:31:52.174 --> 00:31:52.995 because I think

NOTE Confidence: 0.960422

00:31:53.455 --> 00:31:56.015 perhaps this, NDA antagonist effect

NOTE Confidence: 0.960422

00:31:56.015 --> 00:31:57.775 would suppress these active cells

NOTE Confidence: 0.960422

00:31:57.775 --> 00:32:00.095 that were active following chronic

NOTE Confidence: 0.960422

00:32:00.095 --> 00:32:00.595 stress,

NOTE Confidence: 0.99010885

00:32:01.615 --> 00:32:02.895 and then maybe the shift

NOTE Confidence: 0.99010885

00:32:02.895 --> 00:32:04.740 in network activity might drive

NOTE Confidence: 0.99010885

00:32:04.900 --> 00:32:05.960 a different population.

NOTE Confidence: 0.9435565

00:32:06.740 --> 00:32:07.700 It turns out I couldn't

NOTE Confidence: 0.9435565

00:32:07.700 --> 00:32:10.120 be, further, from the truth.

NOTE Confidence: 0.9435565

00:32:10.260 --> 00:32:11.540 And so here's a a

NOTE Confidence: 0.9435565

00:32:11.540 --> 00:32:12.820 raw data. So this is

NOTE Confidence: 0.9435565

00:32:12.820 --> 00:32:14.820 a a mouse, following chronic

NOTE Confidence: 0.9435565

00:32:14.820 --> 00:32:15.320 stress.

NOTE Confidence: 0.99463266

00:32:15.620 --> 00:32:17.460 You're looking at these, neurons

NOTE Confidence: 0.99463266

00:32:17.460 --> 00:32:17.960 expressing

NOTE Confidence: 0.34354272

00:32:18.495 --> 00:32:18.995 g

NOTE Confidence: 0.9276821

00:32:19.455 --> 00:32:20.255 chem. You can see them

NOTE Confidence: 0.9276821

00:32:20.255 --> 00:32:21.795 flicker, which means that they're

NOTE Confidence: 0.8184166

00:32:27.535 --> 00:32:28.035 active,

NOTE Confidence: 0.94260263

00:32:29.695 --> 00:32:30.575 and this is in wake

NOTE Confidence: 0.94260263

00:32:30.575 --> 00:32:32.040 light at fifty percent. I'm

NOTE Confidence: 0.94260263

00:32:32.120 --> 00:32:33.000 gonna give it a good

NOTE Confidence: 0.94260263

00:32:33.000 --> 00:32:34.440 ten minutes to fifteen minutes

NOTE Confidence: 0.94260263

00:32:34.440 --> 00:32:35.800 to get to equilibrium in

NOTE Confidence: 0.94260263

00:32:35.800 --> 00:32:37.640 the brain. It probably happens

NOTE Confidence: 0.94260263

00:32:37.640 --> 00:32:39.240 much faster than that, but

NOTE Confidence: 0.94260263

00:32:39.240 --> 00:32:40.680 I don't quite know the

NOTE Confidence: 0.94260263

00:32:40.680 --> 00:32:42.600 concentration of nitrous oxide in

NOTE Confidence: 0.94260263

00:32:42.600 --> 00:32:43.580 a mouse brain.

NOTE Confidence: 0.9957466

00:32:45.080 --> 00:32:46.860 And so this is following

NOTE Confidence: 0.7236185

00:32:53.455 --> 00:32:54.755 is following equilibrium

NOTE Confidence: 0.86785084

00:32:55.135 --> 00:32:56.495 of nitrous oxide. You could

NOTE Confidence: 0.86785084

00:32:56.495 --> 00:32:57.775 see there's a sudden active

NOTE Confidence: 0.86785084

00:32:57.775 --> 00:32:58.995 right and sustained,

NOTE Confidence: 0.90636075

00:32:59.855 --> 00:33:00.335 and,

NOTE Confidence: 0.9864844

00:33:00.769 --> 00:33:02.210 this was obviously very, very

NOTE Confidence: 0.9864844

00:33:02.210 --> 00:33:03.409 surprising. You could see, like,

NOTE Confidence: 0.9864844

00:33:03.409 --> 00:33:05.110 these little dots here,

NOTE Confidence: 0.9741402

00:33:05.490 --> 00:33:06.610 also flickering, and those are

NOTE Confidence: 0.9741402

00:33:06.610 --> 00:33:08.450 their apical dendrites. As these

NOTE Confidence: 0.9741402

00:33:08.450 --> 00:33:09.750 cells fire, they also,

NOTE Confidence: 0.8714172

00:33:10.769 --> 00:33:12.070 can fire their dendrites.

NOTE Confidence: 0.9564867

00:33:13.250 --> 00:33:14.610 And so this was,

NOTE Confidence: 0.9842117

00:33:15.250 --> 00:33:16.149 quite shocking.

NOTE Confidence: 0.82162046

00:33:22.105 --> 00:33:23.085 If you pseudo

NOTE Confidence: 0.7614489

00:33:23.625 --> 00:33:24.345 color them

NOTE Confidence: 0.9418775

00:33:26.665 --> 00:33:28.745 and show wakefulness activity in

NOTE Confidence: 0.9418775

00:33:28.745 --> 00:33:30.390 yellow and nitrous oxide in

NOTE Confidence: 0.9418775

00:33:30.470 --> 00:33:31.510 and blue, you could see

NOTE Confidence: 0.9418775

00:33:31.510 --> 00:33:33.130 this really widespread activation

NOTE Confidence: 0.9977479

00:33:33.670 --> 00:33:34.950 as opposed to what's seen

NOTE Confidence: 0.9977479

00:33:34.950 --> 00:33:35.610 in wakefulness.

NOTE Confidence: 0.8693696

00:33:37.750 --> 00:33:38.490 And here,

NOTE Confidence: 0.9676127

00:33:39.510 --> 00:33:40.870 I've given you a pretty

NOTE Confidence: 0.9676127

00:33:40.870 --> 00:33:41.190 good,

NOTE Confidence: 0.9593514

00:33:43.585 --> 00:33:44.865 display of activity in layer

NOTE Confidence: 0.9593514

00:33:44.865 --> 00:33:46.304 two three here and layer

NOTE Confidence: 0.9593514

00:33:46.304 --> 00:33:47.924 five. You could see comparing

NOTE Confidence: 0.9593514

00:33:47.985 --> 00:33:50.065 controls to chronic stress groups,

NOTE Confidence: 0.9593514

00:33:50.065 --> 00:33:51.265 you could see that chronic

NOTE Confidence: 0.9593514

00:33:51.265 --> 00:33:52.804 stress induces a hypoactive

NOTE Confidence: 0.9553988

00:33:53.105 --> 00:33:54.385 state in these neurons in

NOTE Confidence: 0.9553988

00:33:54.385 --> 00:33:55.345 layer two three and layer

NOTE Confidence: 0.9553988

00:33:55.345 --> 00:33:56.965 five, and that's not terribly

NOTE Confidence: 0.9553988

00:33:57.105 --> 00:33:57.985 surprising. That's,

NOTE Confidence: 0.9900694

00:33:58.679 --> 00:33:59.799 been shown over and over

NOTE Confidence: 0.9900694

00:33:59.799 --> 00:34:01.899 again as, chronic stress induces

NOTE Confidence: 0.9900694

00:34:01.960 --> 00:34:02.940 synaptic loss.

NOTE Confidence: 0.94793004

00:34:04.360 --> 00:34:05.879 And what's really interesting is

NOTE Confidence: 0.94793004

00:34:05.879 --> 00:34:07.159 that when you give nitrous

NOTE Confidence: 0.94793004

00:34:07.159 --> 00:34:09.400 oxide, there's robust activation of

NOTE Confidence: 0.94793004

00:34:09.400 --> 00:34:10.520 layer five. You could see

NOTE Confidence: 0.94793004

00:34:10.520 --> 00:34:11.719 this in even the control

NOTE Confidence: 0.94793004

00:34:11.719 --> 00:34:12.219 group

NOTE Confidence: 0.980855

00:34:12.565 --> 00:34:13.605 as well as the chronic

NOTE Confidence: 0.980855

00:34:13.605 --> 00:34:14.505 stress groups.

NOTE Confidence: 0.9824679

00:34:15.285 --> 00:34:16.085 But you don't really see

NOTE Confidence: 0.9824679

00:34:16.085 --> 00:34:17.285 much in layer two three,

NOTE Confidence: 0.9824679

00:34:17.285 --> 00:34:18.245 and that was very, very

NOTE Confidence: 0.9824679

00:34:18.245 --> 00:34:20.085 curious to me, because that,

NOTE Confidence: 0.9824679

00:34:20.245 --> 00:34:21.525 I couldn't imagine how a

NOTE Confidence: 0.9824679

00:34:21.525 --> 00:34:22.425 small gas,

NOTE Confidence: 0.9887681

00:34:23.685 --> 00:34:24.745 n two o,

NOTE Confidence: 0.90134865

00:34:26.180 --> 00:34:27.480 could show specificity.

NOTE Confidence: 0.9204021

00:34:28.980 --> 00:34:30.180 I thought it would, be

NOTE Confidence: 0.9204021

00:34:30.180 --> 00:34:30.420 a,

NOTE Confidence: 0.99769014

00:34:30.980 --> 00:34:32.760 an equal opportunity activator.

NOTE Confidence: 0.97346324

00:34:34.579 --> 00:34:35.940 And, also, I was wasn't

NOTE Confidence: 0.97346324

00:34:35.940 --> 00:34:37.460 sure what fifty percent nitrous

NOTE Confidence: 0.97346324

00:34:37.460 --> 00:34:38.920 oxide meant to a rodent.

NOTE Confidence: 0.9765002

00:34:39.275 --> 00:34:40.395 I knew I couldn't induce

NOTE Confidence: 0.9765002

00:34:40.395 --> 00:34:42.155 anesthesia with fifty percent nitrous

NOTE Confidence: 0.9765002

00:34:42.155 --> 00:34:43.275 oxide because that because that

NOTE Confidence: 0.9765002

00:34:43.275 --> 00:34:44.155 can't be done with a

NOTE Confidence: 0.9765002

00:34:44.155 --> 00:34:45.835 human. But here, I devised

NOTE Confidence: 0.9765002

00:34:45.835 --> 00:34:47.035 a simple experiment where I

NOTE Confidence: 0.9765002

00:34:47.035 --> 00:34:47.535 exposed,

NOTE Confidence: 0.9665406

00:34:48.235 --> 00:34:49.835 either oxygen or nitrous oxide

NOTE Confidence: 0.9665406

00:34:49.835 --> 00:34:50.875 at fifty percent in a

NOTE Confidence: 0.9665406

00:34:50.875 --> 00:34:51.375 closed

NOTE Confidence: 0.8718786

00:34:51.755 --> 00:34:53.775 chamber and monitored the animal's

NOTE Confidence: 0.9721366

00:34:54.450 --> 00:34:55.810 overall gross movement. And what

NOTE Confidence: 0.9721366

00:34:55.810 --> 00:34:56.950 you find is that

NOTE Confidence: 0.98072445

00:34:57.650 --> 00:34:59.330 at fifty percent nitrous oxide,

NOTE Confidence: 0.98072445

00:34:59.330 --> 00:35:00.690 the mice move a lot.

NOTE Confidence: 0.98072445

00:35:00.690 --> 00:35:02.050 There's a lot more distance

NOTE Confidence: 0.98072445

00:35:02.050 --> 00:35:03.670 traveled. Their speed is increased,

NOTE Confidence: 0.943461

00:35:04.690 --> 00:35:05.730 but not necessarily their max

NOTE Confidence: 0.943461

00:35:05.730 --> 00:35:06.735 speed. And these sort of

NOTE Confidence: 0.943461

00:35:07.055 --> 00:35:08.655 upper deflections and these traces

NOTE Confidence: 0.943461

00:35:08.655 --> 00:35:09.395 are exploratory

NOTE Confidence: 0.9129565

00:35:09.695 --> 00:35:10.815 events. So it seems that

NOTE Confidence: 0.9129565

00:35:10.815 --> 00:35:12.015 the mouse is engaged in

NOTE Confidence: 0.9129565

00:35:12.015 --> 00:35:14.035 its environment and exploring more,

NOTE Confidence: 0.9989338

00:35:14.895 --> 00:35:16.515 but they're definitely not sedated

NOTE Confidence: 0.9989338

00:35:16.735 --> 00:35:18.015 in any way under this

NOTE Confidence: 0.9989338

00:35:18.015 --> 00:35:18.515 dose.

NOTE Confidence: 0.9947112

00:35:19.520 --> 00:35:21.040 And what I wanna really,

NOTE Confidence: 0.99745935

00:35:21.680 --> 00:35:23.380 emphasize here is this particular

NOTE Confidence: 0.99745935

00:35:23.440 --> 00:35:24.719 slide, which I think is

NOTE Confidence: 0.99745935

00:35:24.719 --> 00:35:25.619 rather amazing.

NOTE Confidence: 0.99196464

00:35:26.079 --> 00:35:26.960 And so if you look

NOTE Confidence: 0.99196464

00:35:26.960 --> 00:35:28.320 at these layer five neurons

NOTE Confidence: 0.99196464

00:35:28.320 --> 00:35:29.520 and looking at their calcium

NOTE Confidence: 0.99196464

00:35:29.520 --> 00:35:31.200 activity over time, you could

NOTE Confidence: 0.99196464

00:35:31.200 --> 00:35:33.040 see that nitrous oxide activates

NOTE Confidence: 0.99196464

00:35:33.040 --> 00:35:33.540 them.

NOTE Confidence: 0.98656845

00:35:33.915 --> 00:35:34.955 And then I'm gonna blow

NOTE Confidence: 0.98656845

00:35:34.955 --> 00:35:36.475 off all this gas, and

NOTE Confidence: 0.98656845

00:35:36.475 --> 00:35:37.675 then I'm gonna revisit these

NOTE Confidence: 0.98656845

00:35:37.675 --> 00:35:39.295 same neurons an hour later.

NOTE Confidence: 0.99238384

00:35:39.594 --> 00:35:40.715 And so there's no drug

NOTE Confidence: 0.99238384

00:35:40.715 --> 00:35:41.835 in the system, but when

NOTE Confidence: 0.99238384

00:35:41.835 --> 00:35:43.055 you look at their activity,

NOTE Confidence: 0.9995949

00:35:43.355 --> 00:35:44.175 they're profoundly

NOTE Confidence: 0.94612336

00:35:44.555 --> 00:35:44.955 active.

NOTE Confidence: 0.968496

00:35:46.140 --> 00:35:47.339 And that's true in the

NOTE Confidence: 0.968496

00:35:47.339 --> 00:35:47.839 control.

NOTE Confidence: 0.9684723

00:35:48.140 --> 00:35:49.819 It's also true in the,

NOTE Confidence: 0.9684723

00:35:50.140 --> 00:35:51.119 chronic stress,

NOTE Confidence: 0.99777484

00:35:52.619 --> 00:35:53.119 cohorts.

NOTE Confidence: 0.92155826

00:35:53.900 --> 00:35:54.640 And interestingly,

NOTE Confidence: 0.9536425

00:35:55.019 --> 00:35:56.380 if you now go back

NOTE Confidence: 0.9536425

00:35:56.380 --> 00:35:58.319 and reimage layer two three,

NOTE Confidence: 0.9536425

00:35:58.539 --> 00:35:59.694 what you find is all

NOTE Confidence: 0.9536425

00:35:59.694 --> 00:36:01.295 of a sudden, re layer

NOTE Confidence: 0.9536425

00:36:01.295 --> 00:36:02.035 two three,

NOTE Confidence: 0.95613825

00:36:03.214 --> 00:36:05.214 is is now active, which

NOTE Confidence: 0.95613825

00:36:05.214 --> 00:36:06.895 when they previously weren't active

NOTE Confidence: 0.95613825

00:36:06.895 --> 00:36:08.655 under the drug treatment. So

NOTE Confidence: 0.95613825

00:36:08.655 --> 00:36:10.275 it's as if layer five,

NOTE Confidence: 0.9920382

00:36:11.055 --> 00:36:12.734 was recruited during the drug

NOTE Confidence: 0.9920382

00:36:12.734 --> 00:36:13.234 treatment,

NOTE Confidence: 0.9393921

00:36:14.070 --> 00:36:16.070 displayed persistent activity following the

NOTE Confidence: 0.9393921

00:36:16.070 --> 00:36:16.890 drug treatment.

NOTE Confidence: 0.9723515

00:36:17.190 --> 00:36:19.110 That persistent activity following the

NOTE Confidence: 0.9723515

00:36:19.110 --> 00:36:19.850 drug treatment,

NOTE Confidence: 0.99378973

00:36:20.950 --> 00:36:21.450 reawakens

NOTE Confidence: 0.93796384

00:36:21.830 --> 00:36:23.110 layer two three. And so

NOTE Confidence: 0.93796384

00:36:23.110 --> 00:36:23.910 now the

NOTE Confidence: 0.9994036

00:36:24.390 --> 00:36:24.890 both

NOTE Confidence: 0.9814155

00:36:25.270 --> 00:36:26.469 sort of the output layer,

NOTE Confidence: 0.9814155

00:36:26.469 --> 00:36:27.430 which is layer five, and

NOTE Confidence: 0.9814155

00:36:27.430 --> 00:36:27.930 also

NOTE Confidence: 0.89824647

00:36:29.895 --> 00:36:31.735 integrator layer, layer two three,

NOTE Confidence: 0.89824647

00:36:31.735 --> 00:36:32.375 is now,

NOTE Confidence: 0.8940433

00:36:32.855 --> 00:36:33.355 recruited,

NOTE Confidence: 0.97774917

00:36:34.215 --> 00:36:35.575 following the treatment. This is

NOTE Confidence: 0.97774917

00:36:35.575 --> 00:36:36.315 the analysis.

NOTE Confidence: 0.9996106

00:36:37.015 --> 00:36:38.475 And to really get at

NOTE Confidence: 0.96578515

00:36:38.855 --> 00:36:39.815 and I and I really

NOTE Confidence: 0.96578515

00:36:39.815 --> 00:36:41.550 became fascinated is how these

NOTE Confidence: 0.96578515

00:36:41.550 --> 00:36:43.390 neurons are activating and why

NOTE Confidence: 0.96578515

00:36:43.390 --> 00:36:44.830 are they specific to layer

NOTE Confidence: 0.96578515

00:36:44.830 --> 00:36:45.330 five.

NOTE Confidence: 0.96732867

00:36:45.630 --> 00:36:46.510 And so I turned to

NOTE Confidence: 0.96732867

00:36:46.510 --> 00:36:47.489 some of the,

NOTE Confidence: 0.88525814

00:36:48.670 --> 00:36:49.870 classic work done by the

NOTE Confidence: 0.88525814

00:36:49.870 --> 00:36:51.090 Zwaromski lab,

NOTE Confidence: 0.3850858

00:36:55.316 --> 00:36:55.816 at

NOTE Confidence: 0.38132298

00:36:58.400 --> 00:36:58.900 that

NOTE Confidence: 0.41664898

00:37:01.483 --> 00:37:01.983 that

NOTE Confidence: 0.95673704

00:37:03.025 --> 00:37:03.525 showed

NOTE Confidence: 0.9598075

00:37:04.566 --> 00:37:05.066 that,

NOTE Confidence: 0.99934113

00:37:06.108 --> 00:37:06.608 again,

NOTE Confidence: 0.8457429

00:37:07.809 --> 00:37:09.670 this is in, cultured neurons,

NOTE Confidence: 0.9681195

00:37:10.609 --> 00:37:12.210 like, if nitrous oxide is

NOTE Confidence: 0.9681195

00:37:12.210 --> 00:37:13.910 working through the NMDA receptor.

NOTE Confidence: 0.96082383

00:37:15.569 --> 00:37:17.010 And here you're looking at

NOTE Confidence: 0.96082383

00:37:17.010 --> 00:37:17.510 activity,

NOTE Confidence: 0.89845777

00:37:18.130 --> 00:37:18.869 in wakefulness,

NOTE Confidence: 0.9409857

00:37:19.250 --> 00:37:20.710 and then I'm gonna

NOTE Confidence: 0.93638045

00:37:21.089 --> 00:37:21.589 locally

NOTE Confidence: 0.67950153

00:37:24.425 --> 00:37:26.265 use an MDA antagonist, which

NOTE Confidence: 0.67950153

00:37:26.265 --> 00:37:27.565 was MKO. You find

NOTE Confidence: 0.8892796

00:37:28.105 --> 00:37:30.105 the typical of MKO one,

NOTE Confidence: 0.8892796

00:37:30.105 --> 00:37:31.785 you're gonna actually suppress calcium

NOTE Confidence: 0.8892796

00:37:31.785 --> 00:37:32.285 activity.

NOTE Confidence: 0.95196205

00:37:33.065 --> 00:37:34.185 And then if you then

NOTE Confidence: 0.95196205

00:37:34.185 --> 00:37:35.705 record these neurons under nitrous

NOTE Confidence: 0.95196205

00:37:35.705 --> 00:37:37.290 oxide, you can activate them.

NOTE Confidence: 0.95196205

00:37:37.370 --> 00:37:38.650 My prediction was is that

NOTE Confidence: 0.95196205

00:37:38.650 --> 00:37:40.090 they should stay silent, if

NOTE Confidence: 0.95196205

00:37:40.090 --> 00:37:41.230 not silence more.

NOTE Confidence: 0.9734248

00:37:42.730 --> 00:37:44.170 And then furthermore, if you

NOTE Confidence: 0.9734248

00:37:44.170 --> 00:37:45.530 perform a, like, a rather

NOTE Confidence: 0.9734248

00:37:45.530 --> 00:37:46.969 full synaptic block and you

NOTE Confidence: 0.9734248

00:37:46.969 --> 00:37:47.469 inhibit

NOTE Confidence: 0.95950204

00:37:48.410 --> 00:37:50.330 AMPA receptors, you could see

NOTE Confidence: 0.95950204

00:37:50.330 --> 00:37:52.114 the effect of, of the

NOTE Confidence: 0.95950204

00:37:52.194 --> 00:37:53.094 this pharmacological

NOTE Confidence: 0.96484077

00:37:53.954 --> 00:37:54.454 treatment.

NOTE Confidence: 0.9418027

00:37:55.075 --> 00:37:56.214 And then if

NOTE Confidence: 0.88498956

00:37:58.594 --> 00:38:00.275 you give nitrous oxide, you

NOTE Confidence: 0.88498956

00:38:00.275 --> 00:38:01.395 could still act it, sort

NOTE Confidence: 0.88498956

00:38:01.395 --> 00:38:03.175 of almost like synaptic independent

NOTE Confidence: 0.88498956

00:38:03.395 --> 00:38:03.895 mechanism

NOTE Confidence: 0.9946723

00:38:05.109 --> 00:38:06.550 here. Here's a movie to

NOTE Confidence: 0.9946723

00:38:06.550 --> 00:38:08.410 sort of, keep you interested.

NOTE Confidence: 0.999775

00:38:09.030 --> 00:38:10.410 I'm recording spontaneous

NOTE Confidence: 0.90618426

00:38:10.710 --> 00:38:11.690 activity wakefulness.

NOTE Confidence: 0.94315505

00:38:12.469 --> 00:38:13.670 This is again layer five,

NOTE Confidence: 0.94315505

00:38:13.670 --> 00:38:14.950 sort of deep within layer

NOTE Confidence: 0.94315505

00:38:14.950 --> 00:38:15.450 five.

NOTE Confidence: 0.93229896

00:38:15.910 --> 00:38:16.869 You could see these neurons

NOTE Confidence: 0.93229896

00:38:16.869 --> 00:38:17.369 activating.

NOTE Confidence: 0.9892134

00:38:17.765 --> 00:38:19.364 Then I'm gonna expose nitrous

NOTE Confidence: 0.9892134

00:38:19.364 --> 00:38:21.045 oxide at fifty percent. The

NOTE Confidence: 0.9892134

00:38:21.045 --> 00:38:22.245 prediction is they're gonna be

NOTE Confidence: 0.9892134

00:38:22.245 --> 00:38:23.844 activated, and when they're activated,

NOTE Confidence: 0.9892134

00:38:23.844 --> 00:38:24.905 they're in a very

NOTE Confidence: 0.9997254

00:38:25.364 --> 00:38:25.864 robust

NOTE Confidence: 0.84176767

00:38:32.400 --> 00:38:34.080 regimen of firing, maybe burst

NOTE Confidence: 0.84176767

00:38:34.080 --> 00:38:35.680 firing. And then the ten,

NOTE Confidence: 0.84176767

00:38:35.680 --> 00:38:36.980 you could see it's actually,

NOTE Confidence: 0.9042587

00:38:37.440 --> 00:38:38.260 quite different.

NOTE Confidence: 0.96471024

00:38:39.120 --> 00:38:40.960 And the activity is rather

NOTE Confidence: 0.96471024

00:38:40.960 --> 00:38:42.400 sustained, but in a more,

NOTE Confidence: 0.99894875

00:38:42.719 --> 00:38:43.219 modest

NOTE Confidence: 0.9867209

00:38:44.454 --> 00:38:44.954 way.

NOTE Confidence: 0.9702719

00:38:45.494 --> 00:38:47.094 And so in this work,

NOTE Confidence: 0.9702719

00:38:47.094 --> 00:38:48.855 I really tried to figure

NOTE Confidence: 0.9702719

00:38:48.855 --> 00:38:50.775 out how nitrous oxide could

NOTE Confidence: 0.9702719

00:38:50.775 --> 00:38:52.315 recruit these layer five neurons.

NOTE Confidence: 0.99882257

00:38:52.694 --> 00:38:54.075 And as you might imagine,

NOTE Confidence: 0.9827965

00:38:55.255 --> 00:38:56.155 all being neuroscientists,

NOTE Confidence: 0.97316074

00:38:56.614 --> 00:38:57.994 that there are many possibilities.

NOTE Confidence: 0.97316074

00:38:58.135 --> 00:38:58.900 There There could be changes

NOTE Confidence: 0.97316074

00:38:58.900 --> 00:39:00.180 in synaptic input. There could

NOTE Confidence: 0.97316074

00:39:00.180 --> 00:39:01.719 be changes in intergenic integration.

NOTE Confidence: 0.97316074

00:39:01.940 --> 00:39:03.460 Inhibition could change. You could

NOTE Confidence: 0.97316074

00:39:03.460 --> 00:39:04.900 have various different types of

NOTE Confidence: 0.97316074

00:39:04.900 --> 00:39:05.880 activating channels.

NOTE Confidence: 0.9934636

00:39:07.140 --> 00:39:08.580 You could begin to open

NOTE Confidence: 0.9934636

00:39:08.580 --> 00:39:09.080 intracellular

NOTE Confidence: 0.8511537

00:39:09.380 --> 00:39:10.760 stores that'll leak calcium,

NOTE Confidence: 0.99834687

00:39:11.195 --> 00:39:12.015 or you could

NOTE Confidence: 0.9106796

00:39:12.395 --> 00:39:13.915 have more classic changes in

NOTE Confidence: 0.9106796

00:39:13.915 --> 00:39:16.175 neuro excitability through, say, potassium

NOTE Confidence: 0.9106796

00:39:16.235 --> 00:39:16.735 channels.

NOTE Confidence: 0.9990946

00:39:18.315 --> 00:39:19.675 And so I won't be

NOTE Confidence: 0.9990946

00:39:19.675 --> 00:39:20.795 able to show you all

NOTE Confidence: 0.9990946

00:39:20.795 --> 00:39:22.315 of these possibilities, but I

NOTE Confidence: 0.9990946

00:39:22.315 --> 00:39:23.935 thoroughly thought about them

NOTE Confidence: 0.97116977

00:39:26.250 --> 00:39:27.210 as I went through this

NOTE Confidence: 0.97116977

00:39:27.210 --> 00:39:28.890 work. And so here, you're

NOTE Confidence: 0.97116977

00:39:28.890 --> 00:39:29.450 looking at,

NOTE Confidence: 0.99099857

00:39:30.090 --> 00:39:32.190 synapses here in the apical

NOTE Confidence: 0.96192265

00:39:32.650 --> 00:39:33.770 tuft of a layer five

NOTE Confidence: 0.96192265

00:39:33.770 --> 00:39:34.270 neuron,

NOTE Confidence: 0.9637784

00:39:34.810 --> 00:39:36.410 and we can detect these

NOTE Confidence: 0.9637784

00:39:36.410 --> 00:39:37.469 synaptic events,

NOTE Confidence: 0.93801445

00:39:38.685 --> 00:39:40.285 by using calcium indicators like

NOTE Confidence: 0.93801445

00:39:40.285 --> 00:39:41.265 I showed you before.

NOTE Confidence: 0.9572549

00:39:41.565 --> 00:39:42.125 And when you,

NOTE Confidence: 0.96359587

00:39:42.685 --> 00:39:44.125 turn on nitrous oxide or

NOTE Confidence: 0.96359587

00:39:44.125 --> 00:39:45.405 record under nitrous oxide, you

NOTE Confidence: 0.96359587

00:39:45.405 --> 00:39:46.445 don't really see much in

NOTE Confidence: 0.96359587

00:39:46.445 --> 00:39:48.605 the way of, recruitment of

NOTE Confidence: 0.96359587

00:39:48.605 --> 00:39:50.525 synapses, which is, again, very

NOTE Confidence: 0.96359587

00:39:50.525 --> 00:39:51.805 curious because you need synaptic

NOTE Confidence: 0.96359587

00:39:51.805 --> 00:39:53.105 input to drive cells.

NOTE Confidence: 0.99227136

00:39:53.700 --> 00:39:55.780 When you also record these

NOTE Confidence: 0.99227136

00:39:55.780 --> 00:39:58.119 apical dendrites, they produce these

NOTE Confidence: 0.99227136

00:39:58.180 --> 00:39:59.880 fantastic calcium nonlinear

NOTE Confidence: 0.769133

00:40:00.260 --> 00:40:00.760 nonlinearities.

NOTE Confidence: 0.98736495

00:40:02.339 --> 00:40:04.339 And, under nitrous oxide, you

NOTE Confidence: 0.98736495

00:40:04.339 --> 00:40:06.420 don't see them, occurring. And

NOTE Confidence: 0.98736495

00:40:06.420 --> 00:40:07.780 the presence of these types

NOTE Confidence: 0.98736495

00:40:07.780 --> 00:40:08.839 of dendritic

NOTE Confidence: 0.9809489

00:40:09.265 --> 00:40:10.965 spikes, so called dendritic spikes,

NOTE Confidence: 0.9809489

00:40:11.025 --> 00:40:12.705 would also give rise to,

NOTE Confidence: 0.99933755

00:40:13.425 --> 00:40:14.165 the activation

NOTE Confidence: 0.9640463

00:40:14.465 --> 00:40:15.665 of the of the cell

NOTE Confidence: 0.9640463

00:40:15.665 --> 00:40:16.864 body in layer five, but

NOTE Confidence: 0.9640463

00:40:16.864 --> 00:40:17.984 we don't really quite see

NOTE Confidence: 0.9640463

00:40:17.984 --> 00:40:19.505 that. What you see, again,

NOTE Confidence: 0.9640463

00:40:19.505 --> 00:40:21.025 if you're imaging across this

NOTE Confidence: 0.9640463

00:40:21.025 --> 00:40:22.950 individual neuron, you see that

NOTE Confidence: 0.9640463

00:40:22.950 --> 00:40:24.630 the soma is activated in

NOTE Confidence: 0.9640463

00:40:24.630 --> 00:40:26.010 sort of this burst configuration.

NOTE Confidence: 0.96414435

00:40:27.109 --> 00:40:28.070 And they actually see some

NOTE Confidence: 0.96414435

00:40:28.070 --> 00:40:29.690 calcium activity in the trunk,

NOTE Confidence: 0.94310033

00:40:30.150 --> 00:40:31.190 deep down, and this might

NOTE Confidence: 0.94310033

00:40:31.190 --> 00:40:32.489 be really the two backpropagating

NOTE Confidence: 0.9885939

00:40:33.270 --> 00:40:34.969 action potentials in these particular

NOTE Confidence: 0.9885939

00:40:35.030 --> 00:40:35.530 neurons.

NOTE Confidence: 0.9975931

00:40:37.045 --> 00:40:37.705 And then,

NOTE Confidence: 0.99136615

00:40:38.325 --> 00:40:39.065 I became,

NOTE Confidence: 0.9751519

00:40:40.485 --> 00:40:41.145 sort of,

NOTE Confidence: 0.9883491

00:40:41.765 --> 00:40:43.045 not convinced, but I wanted

NOTE Confidence: 0.9883491

00:40:43.045 --> 00:40:44.405 to prove to myself with

NOTE Confidence: 0.9883491

00:40:44.405 --> 00:40:45.525 a little bit more certainty

NOTE Confidence: 0.9883491

00:40:45.525 --> 00:40:47.225 that these apical tough dendrites

NOTE Confidence: 0.9883491

00:40:47.285 --> 00:40:48.725 don't really contribute to these

NOTE Confidence: 0.9883491

00:40:48.725 --> 00:40:49.225 somatic,

NOTE Confidence: 0.99100864

00:40:49.850 --> 00:40:50.830 calcium events.

NOTE Confidence: 0.98880243

00:40:51.130 --> 00:40:52.270 And so in this experiment,

NOTE Confidence: 0.98880243

00:40:52.330 --> 00:40:53.290 I can record at two

NOTE Confidence: 0.98880243

00:40:53.290 --> 00:40:54.170 different layers,

NOTE Confidence: 0.9034794

00:40:54.570 --> 00:40:55.770 superficial layer and a deep

NOTE Confidence: 0.9034794

00:40:55.770 --> 00:40:56.270 layer,

NOTE Confidence: 0.9935807

00:40:56.969 --> 00:40:58.090 and I can see them

NOTE Confidence: 0.9935807

00:40:58.090 --> 00:40:59.710 activate under nitrous oxide.

NOTE Confidence: 0.9764039

00:41:00.810 --> 00:41:02.090 But what I then did

NOTE Confidence: 0.9764039

00:41:02.090 --> 00:41:03.370 is I then used the

NOTE Confidence: 0.9764039

00:41:03.370 --> 00:41:04.785 two photon laser to cut

NOTE Confidence: 0.9764039

00:41:04.785 --> 00:41:06.645 the dendrite and completely sever

NOTE Confidence: 0.9764039

00:41:06.944 --> 00:41:07.344 these,

NOTE Confidence: 0.99376065

00:41:07.984 --> 00:41:09.505 these apical tufts from their

NOTE Confidence: 0.99376065

00:41:09.505 --> 00:41:10.325 parent dendrite.

NOTE Confidence: 0.9912284

00:41:11.025 --> 00:41:12.224 And so in this particular

NOTE Confidence: 0.9912284

00:41:12.224 --> 00:41:14.065 example, I performed two cuts

NOTE Confidence: 0.9912284

00:41:14.065 --> 00:41:15.204 across this dendrite,

NOTE Confidence: 0.93942136

00:41:16.385 --> 00:41:17.505 completely, and then you could

NOTE Confidence: 0.93942136

00:41:17.505 --> 00:41:18.640 see the beating of the

NOTE Confidence: 0.93942136

00:41:18.640 --> 00:41:20.160 dendrite here suggesting that it's

NOTE Confidence: 0.93942136

00:41:20.160 --> 00:41:21.060 a clean break,

NOTE Confidence: 0.9625546

00:41:21.680 --> 00:41:23.859 and dendritic signals of loss,

NOTE Confidence: 0.9625546

00:41:24.080 --> 00:41:25.700 but yet the somatic activity

NOTE Confidence: 0.9625546

00:41:25.760 --> 00:41:27.520 persists. So this again suggests

NOTE Confidence: 0.9625546

00:41:27.520 --> 00:41:28.660 that synapses

NOTE Confidence: 0.9992513

00:41:29.040 --> 00:41:29.780 are probably

NOTE Confidence: 0.9996644

00:41:30.160 --> 00:41:31.540 not the underlying mechanism

NOTE Confidence: 0.9990139

00:41:31.840 --> 00:41:32.900 driving the activation

NOTE Confidence: 0.99435735

00:41:33.375 --> 00:41:34.575 of these layer five neurons

NOTE Confidence: 0.99435735

00:41:34.575 --> 00:41:35.795 under nitrous oxide.

NOTE Confidence: 0.98095113

00:41:37.375 --> 00:41:38.335 In in the quest to

NOTE Confidence: 0.98095113

00:41:38.335 --> 00:41:40.415 figure out how can I,

NOTE Confidence: 0.9992876

00:41:40.975 --> 00:41:43.395 modulate this layer five activity,

NOTE Confidence: 0.970012

00:41:43.775 --> 00:41:44.735 I then turned to one

NOTE Confidence: 0.970012

00:41:44.735 --> 00:41:46.094 of those earlier experiments where

NOTE Confidence: 0.970012

00:41:46.094 --> 00:41:46.755 I coupled,

NOTE Confidence: 0.8799351

00:41:47.295 --> 00:41:47.795 isofluorine,

NOTE Confidence: 0.98032904

00:41:48.719 --> 00:41:50.020 with nitrous oxide?

NOTE Confidence: 0.9953724

00:41:50.400 --> 00:41:51.619 And what you see here

NOTE Confidence: 0.9953724

00:41:51.680 --> 00:41:53.280 is that nitrous oxide recruits

NOTE Confidence: 0.9953724

00:41:53.280 --> 00:41:54.500 these layer five neurons,

NOTE Confidence: 0.9885059

00:41:55.280 --> 00:41:56.800 but even a small dose

NOTE Confidence: 0.9885059

00:41:56.800 --> 00:41:57.460 of isofluorine.

NOTE Confidence: 0.977091

00:41:58.160 --> 00:41:59.040 So this would not be

NOTE Confidence: 0.977091

00:41:59.040 --> 00:42:00.640 considered general anesthesia. This wouldn't

NOTE Confidence: 0.977091

00:42:00.640 --> 00:42:02.000 even be considered sedation. This

NOTE Confidence: 0.977091

00:42:02.000 --> 00:42:02.500 is

NOTE Confidence: 0.8567168

00:42:03.035 --> 00:42:04.395 this is, sub,

NOTE Confidence: 0.9510701

00:42:05.835 --> 00:42:07.035 very subnautic. I don't even

NOTE Confidence: 0.9510701

00:42:07.035 --> 00:42:07.835 know what you would wanna

NOTE Confidence: 0.9510701

00:42:07.835 --> 00:42:08.395 call this. This is a

NOTE Confidence: 0.9510701

00:42:08.395 --> 00:42:09.755 very low dose. This would

NOTE Confidence: 0.9510701

00:42:09.755 --> 00:42:10.735 be, considered,

NOTE Confidence: 0.9219299

00:42:11.114 --> 00:42:12.335 sub hypnotic isoflaurine.

NOTE Confidence: 0.99946296

00:42:13.515 --> 00:42:15.035 One point two percent is

NOTE Confidence: 0.99946296

00:42:15.035 --> 00:42:16.495 considered hypnotic isoflaurine.

NOTE Confidence: 0.9927768

00:42:16.860 --> 00:42:18.000 You could see that activity

NOTE Confidence: 0.9927768

00:42:18.220 --> 00:42:19.520 is completely lost.

NOTE Confidence: 0.95081615

00:42:19.980 --> 00:42:20.700 And then if you look

NOTE Confidence: 0.95081615

00:42:20.700 --> 00:42:22.320 at the behavior, its antidepressant

NOTE Confidence: 0.98869985

00:42:22.860 --> 00:42:23.980 effect is lost when you

NOTE Confidence: 0.98869985

00:42:23.980 --> 00:42:26.140 couple this with isofluorane. So,

NOTE Confidence: 0.98869985

00:42:26.140 --> 00:42:27.980 again, this is separate evidence

NOTE Confidence: 0.98869985

00:42:27.980 --> 00:42:29.100 with a different type of

NOTE Confidence: 0.98869985

00:42:29.100 --> 00:42:31.120 anesthetic that has psychedelic properties

NOTE Confidence: 0.9723043

00:42:31.420 --> 00:42:33.045 that if you couple nitrous

NOTE Confidence: 0.9723043

00:42:33.045 --> 00:42:34.964 oxide or even ketamine to

NOTE Confidence: 0.9723043

00:42:34.964 --> 00:42:35.944 sort of a GABAergic

NOTE Confidence: 0.998444

00:42:36.244 --> 00:42:36.744 anesthetic,

NOTE Confidence: 0.99505955

00:42:37.285 --> 00:42:38.885 you begin to eliminate some

NOTE Confidence: 0.99505955

00:42:38.885 --> 00:42:40.425 of its activity profile

NOTE Confidence: 0.9786112

00:42:40.885 --> 00:42:42.585 and also behavioral effects.

NOTE Confidence: 0.9934397

00:42:43.925 --> 00:42:45.670 And so in this,

NOTE Confidence: 0.9661584

00:42:46.210 --> 00:42:47.170 part of the talk, I've

NOTE Confidence: 0.9661584

00:42:47.170 --> 00:42:48.450 really told you that nitrous

NOTE Confidence: 0.9661584

00:42:48.450 --> 00:42:50.130 oxide recruits layer five, and

NOTE Confidence: 0.9661584

00:42:50.130 --> 00:42:51.890 this is quite surprising consider

NOTE Confidence: 0.9661584

00:42:51.890 --> 00:42:53.270 this gas is everywhere

NOTE Confidence: 0.9729341

00:42:53.570 --> 00:42:55.090 at a high concentration, which

NOTE Confidence: 0.9729341

00:42:55.090 --> 00:42:56.150 is fifty percent,

NOTE Confidence: 0.98091215

00:42:56.450 --> 00:42:58.130 and that this activity induced

NOTE Confidence: 0.98091215

00:42:58.130 --> 00:42:59.935 by nitrous oxide persists once

NOTE Confidence: 0.98091215

00:42:59.935 --> 00:43:00.994 the drug is eliminated,

NOTE Confidence: 0.9908287

00:43:01.614 --> 00:43:02.974 and layer five is required

NOTE Confidence: 0.9908287

00:43:02.974 --> 00:43:03.954 for its antidepressant

NOTE Confidence: 0.9974718

00:43:04.255 --> 00:43:04.915 like effects.

NOTE Confidence: 0.97670454

00:43:05.855 --> 00:43:07.135 And I've also showed you

NOTE Confidence: 0.97670454

00:43:07.135 --> 00:43:08.815 that nitrous oxide doesn't seem

NOTE Confidence: 0.97670454

00:43:08.815 --> 00:43:10.094 to behave like an NMD

NOTE Confidence: 0.97670454

00:43:10.094 --> 00:43:10.594 antagonist

NOTE Confidence: 0.95132643

00:43:11.214 --> 00:43:13.055 as, I've defined an NMD

NOTE Confidence: 0.95132643

00:43:13.055 --> 00:43:14.760 antagonist in others, and it's

NOTE Confidence: 0.95132643

00:43:14.760 --> 00:43:16.140 quite sensitive to anesthesia.

NOTE Confidence: 0.9818104

00:43:17.000 --> 00:43:18.600 And so I wanna conclude

NOTE Confidence: 0.9818104

00:43:18.600 --> 00:43:19.640 with this. I I and

NOTE Confidence: 0.9818104

00:43:19.640 --> 00:43:20.380 I evaluated,

NOTE Confidence: 0.9912892

00:43:21.160 --> 00:43:22.520 some of these other components

NOTE Confidence: 0.9912892

00:43:22.520 --> 00:43:23.400 that I won't be able

NOTE Confidence: 0.9912892

00:43:23.400 --> 00:43:25.020 to tell you about and,

NOTE Confidence: 0.9077151

00:43:26.840 --> 00:43:27.719 to to sort of,

NOTE Confidence: 0.9109621

00:43:29.005 --> 00:43:29.505 really,

NOTE Confidence: 0.98055387

00:43:30.685 --> 00:43:32.285 to to figure out how

NOTE Confidence: 0.98055387

00:43:32.285 --> 00:43:33.885 nitrous oxide might recruit layer

NOTE Confidence: 0.98055387

00:43:33.885 --> 00:43:35.484 five, I turned to looking

NOTE Confidence: 0.98055387

00:43:35.484 --> 00:43:35.984 at

NOTE Confidence: 0.9986191

00:43:36.285 --> 00:43:37.265 sodium channels,

NOTE Confidence: 0.91877574

00:43:37.724 --> 00:43:38.705 calcium channels,

NOTE Confidence: 0.916204

00:43:39.165 --> 00:43:40.224 serotonin uptake

NOTE Confidence: 0.99851227

00:43:41.310 --> 00:43:41.810 properties,

NOTE Confidence: 0.994479

00:43:42.830 --> 00:43:45.570 opioid receptors, intracellular calcium release

NOTE Confidence: 0.9719118

00:43:46.030 --> 00:43:46.530 events,

NOTE Confidence: 0.99430496

00:43:47.070 --> 00:43:48.270 by using different type of,

NOTE Confidence: 0.99430496

00:43:48.590 --> 00:43:49.090 pharmacological

NOTE Confidence: 0.9674448

00:43:49.550 --> 00:43:50.910 agents. And all these agents

NOTE Confidence: 0.9674448

00:43:50.910 --> 00:43:52.350 induce changes in layer five

NOTE Confidence: 0.9674448

00:43:52.350 --> 00:43:53.870 activity, which is probably not

NOTE Confidence: 0.9674448

00:43:53.870 --> 00:43:54.370 surprising,

NOTE Confidence: 0.9964238

00:43:54.875 --> 00:43:56.714 but nitrous oxide was still

NOTE Confidence: 0.9964238

00:43:56.714 --> 00:43:58.174 capable of activating,

NOTE Confidence: 0.98528415

00:43:59.114 --> 00:44:00.655 these types of cells, indicating

NOTE Confidence: 0.98528415

00:44:00.714 --> 00:44:02.155 that it's just not working

NOTE Confidence: 0.98528415

00:44:02.155 --> 00:44:03.855 through this particular mechanism.

NOTE Confidence: 0.9563055

00:44:05.594 --> 00:44:06.395 And then I did a

NOTE Confidence: 0.9563055

00:44:06.395 --> 00:44:07.835 deep dive into the Allen

NOTE Confidence: 0.9563055

00:44:07.835 --> 00:44:08.335 Brain

NOTE Confidence: 0.9254025

00:44:08.960 --> 00:44:09.460 sequencing,

NOTE Confidence: 0.93332237

00:44:10.079 --> 00:44:11.140 open source sequencing,

NOTE Confidence: 0.9677279

00:44:11.599 --> 00:44:12.099 database,

NOTE Confidence: 0.9400967

00:44:13.039 --> 00:44:14.719 and used one of their

NOTE Confidence: 0.9400967

00:44:14.719 --> 00:44:16.880 databases to sort of, maybe

NOTE Confidence: 0.9400967

00:44:16.880 --> 00:44:17.380 more

NOTE Confidence: 0.552669

00:44:18.079 --> 00:44:18.579 systematically

NOTE Confidence: 0.7890935

00:44:19.039 --> 00:44:19.539 screen,

NOTE Confidence: 0.9934153

00:44:20.880 --> 00:44:22.355 what might be,

NOTE Confidence: 0.9798559

00:44:22.895 --> 00:44:23.395 upregulated

NOTE Confidence: 0.9927208

00:44:23.775 --> 00:44:25.395 in two particular cell types.

NOTE Confidence: 0.98899233

00:44:25.695 --> 00:44:26.735 And I was looking particularly

NOTE Confidence: 0.98899233

00:44:26.735 --> 00:44:27.855 at layer five, and I

NOTE Confidence: 0.98899233

00:44:27.855 --> 00:44:28.895 was also looking at,

NOTE Confidence: 0.72394323

00:44:29.455 --> 00:44:30.114 a interneuron

NOTE Confidence: 0.9801896

00:44:30.415 --> 00:44:32.015 called VIP. And data I

NOTE Confidence: 0.9801896

00:44:32.015 --> 00:44:32.815 didn't show you is that

NOTE Confidence: 0.9801896

00:44:32.815 --> 00:44:34.495 nitrous oxide also turns on

NOTE Confidence: 0.9801896

00:44:34.495 --> 00:44:35.875 a VIP interneuron,

NOTE Confidence: 0.9986337

00:44:36.489 --> 00:44:37.950 which is thought to underlie

NOTE Confidence: 0.98799217

00:44:38.489 --> 00:44:38.989 disinhibition.

NOTE Confidence: 0.97961617

00:44:40.570 --> 00:44:42.330 And so I identified this,

NOTE Confidence: 0.9707641

00:44:42.730 --> 00:44:44.090 potassium channel. It's a small

NOTE Confidence: 0.9707641

00:44:44.090 --> 00:44:44.590 conductance,

NOTE Confidence: 0.9987898

00:44:45.130 --> 00:44:47.390 calcium activated potassium channel,

NOTE Confidence: 0.9754599

00:44:47.930 --> 00:44:49.050 which has been explored for

NOTE Confidence: 0.9754599

00:44:49.050 --> 00:44:50.565 years and its role in

NOTE Confidence: 0.9754599

00:44:50.565 --> 00:44:51.065 excitability,

NOTE Confidence: 0.98492694

00:44:51.445 --> 00:44:53.145 synaptic transmission, and plasticity.

NOTE Confidence: 0.9849727

00:44:53.844 --> 00:44:55.065 And this, particular

NOTE Confidence: 0.9605917

00:44:55.364 --> 00:44:58.025 potassium channel has, increased transcripts

NOTE Confidence: 0.9605917

00:44:58.085 --> 00:44:59.205 in both these types of

NOTE Confidence: 0.9605917

00:44:59.205 --> 00:45:00.244 cells. So I said, okay.

NOTE Confidence: 0.9605917

00:45:00.244 --> 00:45:01.205 This might be a a

NOTE Confidence: 0.9605917

00:45:01.205 --> 00:45:02.665 a good candidate to explore.

NOTE Confidence: 0.9303891

00:45:03.090 --> 00:45:04.290 And then Allen Brain also

NOTE Confidence: 0.9303891

00:45:04.290 --> 00:45:06.310 has some phenomenal in situ,

NOTE Confidence: 0.9457263

00:45:06.610 --> 00:45:07.830 hybridization data,

NOTE Confidence: 0.9656054

00:45:08.210 --> 00:45:09.810 again, showing you that these,

NOTE Confidence: 0.9913563

00:45:10.210 --> 00:45:10.710 mRNA,

NOTE Confidence: 0.992758

00:45:11.489 --> 00:45:12.850 is located in layer five.

NOTE Confidence: 0.992758

00:45:12.850 --> 00:45:13.730 And then if you look,

NOTE Confidence: 0.992758

00:45:13.730 --> 00:45:15.110 like, a little bit closely

NOTE Confidence: 0.992758

00:45:15.170 --> 00:45:16.290 at these sort of coronal

NOTE Confidence: 0.992758

00:45:16.290 --> 00:45:17.330 slices, you could see that

NOTE Confidence: 0.992758

00:45:17.330 --> 00:45:18.950 there's, these sparse

NOTE Confidence: 0.969964

00:45:19.385 --> 00:45:20.825 cells in layer two three,

NOTE Confidence: 0.969964

00:45:20.825 --> 00:45:22.344 which would most likely be

NOTE Confidence: 0.969964

00:45:22.344 --> 00:45:22.844 these,

NOTE Confidence: 0.9915282

00:45:24.185 --> 00:45:24.685 interneurons.

NOTE Confidence: 0.91896963

00:45:25.385 --> 00:45:26.265 And so I thought this

NOTE Confidence: 0.91896963

00:45:26.265 --> 00:45:28.285 was a a a reasonable,

NOTE Confidence: 0.99905586

00:45:28.825 --> 00:45:30.105 molecule to test a little

NOTE Confidence: 0.99905586

00:45:30.105 --> 00:45:31.005 bit more robustly.

NOTE Confidence: 0.9975666

00:45:31.464 --> 00:45:32.940 And so what this channel

NOTE Confidence: 0.9975666

00:45:32.940 --> 00:45:34.619 does is that this channel

NOTE Confidence: 0.9975666

00:45:34.619 --> 00:45:36.719 really controls the after hyperpolarization.

NOTE Confidence: 0.9969309

00:45:37.660 --> 00:45:39.020 And so when a neuron

NOTE Confidence: 0.9969309

00:45:39.020 --> 00:45:39.520 fires

NOTE Confidence: 0.9995655

00:45:39.900 --> 00:45:41.280 and has calcium entry,

NOTE Confidence: 0.9600136

00:45:41.820 --> 00:45:43.739 this potassium channel interestingly has

NOTE Confidence: 0.9600136

00:45:43.739 --> 00:45:45.280 a calcium sensitive domain.

NOTE Confidence: 0.9554677

00:45:46.105 --> 00:45:47.625 And when it's sensed, it's

NOTE Confidence: 0.9554677

00:45:47.625 --> 00:45:48.105 gonna,

NOTE Confidence: 0.99799556

00:45:48.585 --> 00:45:50.285 activate this channel to efflux

NOTE Confidence: 0.99799556

00:45:50.425 --> 00:45:50.925 potassium

NOTE Confidence: 0.9760637

00:45:51.465 --> 00:45:52.525 and, create

NOTE Confidence: 0.7759017

00:45:52.905 --> 00:45:53.405 a,

NOTE Confidence: 0.9951941

00:45:53.945 --> 00:45:54.445 hyperpolarization

NOTE Confidence: 0.9850318

00:45:55.145 --> 00:45:56.265 and keep that cell from

NOTE Confidence: 0.9850318

00:45:56.265 --> 00:45:57.245 firing further,

NOTE Confidence: 0.9890368

00:45:57.800 --> 00:45:58.300 potentially.

NOTE Confidence: 0.99888444

00:45:58.680 --> 00:45:59.719 If you were to close

NOTE Confidence: 0.99888444

00:45:59.719 --> 00:46:01.400 this channel via a poor

NOTE Confidence: 0.99888444

00:46:01.400 --> 00:46:01.900 mechanism,

NOTE Confidence: 0.987992

00:46:03.560 --> 00:46:05.080 you would reduce this after

NOTE Confidence: 0.987992

00:46:05.080 --> 00:46:05.580 hyperpolarization,

NOTE Confidence: 0.95074284

00:46:06.200 --> 00:46:07.800 keeping the mem keeping the

NOTE Confidence: 0.95074284

00:46:07.800 --> 00:46:09.080 neuron closer to its,

NOTE Confidence: 0.98813903

00:46:09.719 --> 00:46:11.400 threshold for firing, and you

NOTE Confidence: 0.98813903

00:46:11.400 --> 00:46:13.580 might even see, increased firing.

NOTE Confidence: 0.9451755

00:46:14.255 --> 00:46:15.855 And so a decreased s

NOTE Confidence: 0.9451755

00:46:15.855 --> 00:46:17.775 k two, function might lead

NOTE Confidence: 0.9451755

00:46:17.775 --> 00:46:19.555 to, enhanced excitability

NOTE Confidence: 0.99613

00:46:20.255 --> 00:46:20.995 and firing.

NOTE Confidence: 0.98539436

00:46:21.695 --> 00:46:23.235 And so I I,

NOTE Confidence: 0.9263228

00:46:23.695 --> 00:46:25.155 reached out to Chuck Soromsky,

NOTE Confidence: 0.9263228

00:46:25.295 --> 00:46:26.915 the the the the the,

NOTE Confidence: 0.94949913

00:46:27.230 --> 00:46:28.589 you know, very esteemed Chuck

NOTE Confidence: 0.94949913

00:46:28.589 --> 00:46:29.630 Soromski who did some of

NOTE Confidence: 0.94949913

00:46:29.630 --> 00:46:30.130 the

NOTE Confidence: 0.9768664

00:46:30.430 --> 00:46:32.109 classic work on nitrous oxide

NOTE Confidence: 0.9768664

00:46:32.109 --> 00:46:33.309 and said, you know, I

NOTE Confidence: 0.9768664

00:46:33.309 --> 00:46:34.849 presented this data to him,

NOTE Confidence: 0.9768664

00:46:34.910 --> 00:46:36.430 and he was, very much

NOTE Confidence: 0.9768664

00:46:36.430 --> 00:46:37.950 convinced and willing to explore

NOTE Confidence: 0.9768664

00:46:37.950 --> 00:46:38.609 this mechanism,

NOTE Confidence: 0.9493877

00:46:39.885 --> 00:46:41.485 in his preparation. So here,

NOTE Confidence: 0.9493877

00:46:41.485 --> 00:46:42.385 you're looking at,

NOTE Confidence: 0.97606784

00:46:44.045 --> 00:46:45.565 not only the expression that

NOTE Confidence: 0.97606784

00:46:45.565 --> 00:46:46.305 we identified

NOTE Confidence: 0.9245047

00:46:46.765 --> 00:46:47.965 of the angiosus s k

NOTE Confidence: 0.9245047

00:46:47.965 --> 00:46:49.405 two channel here in a

NOTE Confidence: 0.9245047

00:46:49.405 --> 00:46:51.245 a brain slice consisting mostly

NOTE Confidence: 0.9245047

00:46:51.245 --> 00:46:53.005 in layer five and scattered

NOTE Confidence: 0.9245047

00:46:53.005 --> 00:46:54.450 cells in layer two three,

NOTE Confidence: 0.9245047

00:46:54.450 --> 00:46:55.190 But here,

NOTE Confidence: 0.9283051

00:46:55.650 --> 00:46:56.609 when he looks at the

NOTE Confidence: 0.9283051

00:46:56.609 --> 00:46:57.109 after,

NOTE Confidence: 0.995667

00:46:57.650 --> 00:46:58.150 hyperpolarization

NOTE Confidence: 0.98769146

00:46:58.690 --> 00:46:59.190 potential,

NOTE Confidence: 0.9909683

00:47:00.050 --> 00:47:01.650 under baseline and under nitrous

NOTE Confidence: 0.9909683

00:47:01.650 --> 00:47:02.770 oxide, you could see, like

NOTE Confidence: 0.9909683

00:47:02.770 --> 00:47:03.890 I showed in that previous

NOTE Confidence: 0.9909683

00:47:03.890 --> 00:47:05.109 schematic, it's reduced.

NOTE Confidence: 0.9577116

00:47:06.690 --> 00:47:08.130 And this, was a challenging

NOTE Confidence: 0.9577116

00:47:08.130 --> 00:47:09.585 experiment because it's hard to

NOTE Confidence: 0.9577116

00:47:09.665 --> 00:47:10.565 hold a gas,

NOTE Confidence: 0.9884194

00:47:11.665 --> 00:47:13.025 efficiently in a in a

NOTE Confidence: 0.9884194

00:47:13.025 --> 00:47:14.085 brain slice preparation

NOTE Confidence: 0.9459009

00:47:14.545 --> 00:47:15.344 where this,

NOTE Confidence: 0.9592137

00:47:16.464 --> 00:47:17.905 medium has to be infused

NOTE Confidence: 0.9592137

00:47:17.905 --> 00:47:20.385 with a, continuous gas. And

NOTE Confidence: 0.9592137

00:47:20.385 --> 00:47:21.344 if you look at, the

NOTE Confidence: 0.9592137

00:47:21.344 --> 00:47:22.785 control group here, it is

NOTE Confidence: 0.9592137

00:47:22.785 --> 00:47:24.224 is no different from its

NOTE Confidence: 0.9592137

00:47:24.224 --> 00:47:24.724 baseline.

NOTE Confidence: 0.99771875

00:47:25.590 --> 00:47:26.550 So this is a pretty

NOTE Confidence: 0.99771875

00:47:26.550 --> 00:47:28.470 good indicator that nitrous oxide

NOTE Confidence: 0.99771875

00:47:28.470 --> 00:47:30.330 can, inhibit this potential

NOTE Confidence: 0.9879702

00:47:30.950 --> 00:47:32.090 mediated by,

NOTE Confidence: 0.98564297

00:47:32.870 --> 00:47:33.770 s k two.

NOTE Confidence: 0.99739647

00:47:34.230 --> 00:47:35.510 And to sort of put

NOTE Confidence: 0.99739647

00:47:35.510 --> 00:47:36.470 some meat on the bones

NOTE Confidence: 0.99739647

00:47:36.470 --> 00:47:37.350 and to figure out if

NOTE Confidence: 0.99739647

00:47:37.350 --> 00:47:38.810 this is happening in vivo,

NOTE Confidence: 0.99964726

00:47:39.350 --> 00:47:40.090 I started

NOTE Confidence: 0.9996691

00:47:40.455 --> 00:47:41.594 looking at whether

NOTE Confidence: 0.85418624

00:47:41.975 --> 00:47:43.035 SK two inhibition,

NOTE Confidence: 0.97891605

00:47:44.055 --> 00:47:46.135 via pharmacological approach could drive

NOTE Confidence: 0.97891605

00:47:46.135 --> 00:47:47.735 layer five. And so here,

NOTE Confidence: 0.97891605

00:47:47.735 --> 00:47:48.775 you're looking at layer five

NOTE Confidence: 0.97891605

00:47:48.775 --> 00:47:50.135 neurons and also these VIP

NOTE Confidence: 0.97891605

00:47:50.135 --> 00:47:50.635 interneurons,

NOTE Confidence: 0.9833203

00:47:51.415 --> 00:47:52.855 before the drug and after

NOTE Confidence: 0.9833203

00:47:52.855 --> 00:47:53.655 the drug, and you can

NOTE Confidence: 0.9833203

00:47:53.655 --> 00:47:55.035 see that the drug itself

NOTE Confidence: 0.9833203

00:47:55.094 --> 00:47:57.230 can recruit the spontaneous activity

NOTE Confidence: 0.9833203

00:47:57.230 --> 00:47:58.050 of these neurons,

NOTE Confidence: 0.93779117

00:47:58.989 --> 00:48:00.109 and doesn't seem to have

NOTE Confidence: 0.93779117

00:48:00.109 --> 00:48:01.390 an effect in cells that

NOTE Confidence: 0.93779117

00:48:01.390 --> 00:48:02.910 don't have this receptor, such

NOTE Confidence: 0.93779117

00:48:02.910 --> 00:48:04.270 as lamin two three, PV

NOTE Confidence: 0.93779117

00:48:04.270 --> 00:48:05.969 interneurons, or SST interneurons.

NOTE Confidence: 0.99977964

00:48:07.469 --> 00:48:07.969 Moreover,

NOTE Confidence: 0.9839231

00:48:08.270 --> 00:48:09.864 if you put this s

NOTE Confidence: 0.9839231

00:48:09.864 --> 00:48:11.545 k two channel into neurons

NOTE Confidence: 0.9839231

00:48:11.545 --> 00:48:12.985 that don't have the receptor,

NOTE Confidence: 0.9839231

00:48:12.985 --> 00:48:14.505 so now they overexpress this

NOTE Confidence: 0.9839231

00:48:14.505 --> 00:48:16.025 receptor that's not natural to

NOTE Confidence: 0.9839231

00:48:16.025 --> 00:48:17.385 them, you can make them

NOTE Confidence: 0.9839231

00:48:17.385 --> 00:48:19.005 responsive to nitrous oxide.

NOTE Confidence: 0.993772

00:48:19.465 --> 00:48:20.985 Conversely, if you knock down

NOTE Confidence: 0.993772

00:48:20.985 --> 00:48:21.885 s k two

NOTE Confidence: 0.93908215

00:48:23.070 --> 00:48:23.570 protein,

NOTE Confidence: 0.91849434

00:48:24.350 --> 00:48:25.890 inside layer fiber VIP,

NOTE Confidence: 0.9744294

00:48:26.350 --> 00:48:27.230 you render them,

NOTE Confidence: 0.9205816

00:48:27.710 --> 00:48:29.310 mute to nitrous oxide or

NOTE Confidence: 0.9205816

00:48:29.310 --> 00:48:31.070 even apamint, this sort of

NOTE Confidence: 0.9205816

00:48:31.070 --> 00:48:31.570 specific

NOTE Confidence: 0.9868796

00:48:31.870 --> 00:48:33.230 antagonist of s k two

NOTE Confidence: 0.9868796

00:48:33.230 --> 00:48:33.730 channels.

NOTE Confidence: 0.98979515

00:48:35.225 --> 00:48:36.105 And then,

NOTE Confidence: 0.9985508

00:48:36.505 --> 00:48:37.005 because,

NOTE Confidence: 0.9991888

00:48:37.385 --> 00:48:38.105 you know, I'm in a

NOTE Confidence: 0.9991888

00:48:38.105 --> 00:48:39.945 very interesting department that contains

NOTE Confidence: 0.9991888

00:48:39.945 --> 00:48:40.445 neuroscientists

NOTE Confidence: 0.8895936

00:48:40.825 --> 00:48:41.965 but also computational,

NOTE Confidence: 0.96223116

00:48:42.665 --> 00:48:43.165 neurobiologists,

NOTE Confidence: 0.9420593

00:48:43.545 --> 00:48:44.685 I proposed this.

NOTE Confidence: 0.969946

00:48:45.305 --> 00:48:46.985 I, again, presented this data

NOTE Confidence: 0.969946

00:48:46.985 --> 00:48:48.265 to to a fellow colleague

NOTE Confidence: 0.969946

00:48:48.265 --> 00:48:49.325 of mine who does

NOTE Confidence: 0.9740361

00:48:50.330 --> 00:48:51.790 various different types of simulations.

NOTE Confidence: 0.9740361

00:48:51.850 --> 00:48:52.910 And I said, you know,

NOTE Confidence: 0.96478796

00:48:53.210 --> 00:48:54.330 I have this effect of

NOTE Confidence: 0.96478796

00:48:54.330 --> 00:48:56.030 nitrous oxide on this particular

NOTE Confidence: 0.96478796

00:48:56.250 --> 00:48:58.350 type of potassium channel.

NOTE Confidence: 0.9992068

00:48:59.210 --> 00:49:00.730 Is it possible to run

NOTE Confidence: 0.9992068

00:49:00.730 --> 00:49:01.710 some type of

NOTE Confidence: 0.514764

00:49:02.010 --> 00:49:02.510 simulations

NOTE Confidence: 0.99486756

00:49:02.890 --> 00:49:03.550 of this

NOTE Confidence: 0.9775898

00:49:03.924 --> 00:49:05.684 this small drug inside the

NOTE Confidence: 0.9775898

00:49:05.684 --> 00:49:08.184 pore region of this, particular

NOTE Confidence: 0.9775898

00:49:08.244 --> 00:49:08.744 protein.

NOTE Confidence: 0.9659857

00:49:09.204 --> 00:49:10.964 And he did, various different

NOTE Confidence: 0.9659857

00:49:10.964 --> 00:49:12.805 types of calculations that are

NOTE Confidence: 0.9659857

00:49:12.805 --> 00:49:14.085 by far above my pay

NOTE Confidence: 0.9659857

00:49:14.085 --> 00:49:16.005 grade and found that there's

NOTE Confidence: 0.9659857

00:49:16.005 --> 00:49:16.505 indeed,

NOTE Confidence: 0.92353094

00:49:17.045 --> 00:49:18.105 substantial interaction,

NOTE Confidence: 0.94718367

00:49:19.109 --> 00:49:19.509 and,

NOTE Confidence: 0.9690857

00:49:19.910 --> 00:49:21.829 energy changes that would potentially

NOTE Confidence: 0.9690857

00:49:21.829 --> 00:49:23.589 hold nitrous oxide sort of

NOTE Confidence: 0.9690857

00:49:23.589 --> 00:49:24.789 deep within the pore,

NOTE Confidence: 0.8644671

00:49:25.430 --> 00:49:25.930 potentially,

NOTE Confidence: 0.9976649

00:49:26.309 --> 00:49:28.329 creating an inhibition type effect.

NOTE Confidence: 0.98587126

00:49:31.145 --> 00:49:32.505 And so I will,

NOTE Confidence: 0.9754624

00:49:32.984 --> 00:49:34.585 skip this summary slide just

NOTE Confidence: 0.9754624

00:49:34.585 --> 00:49:35.305 so that I have time

NOTE Confidence: 0.9754624

00:49:35.305 --> 00:49:35.964 for questions.

NOTE Confidence: 0.99558604

00:49:37.224 --> 00:49:38.685 And I want to acknowledge,

NOTE Confidence: 0.9723888

00:49:39.065 --> 00:49:40.025 some of the my lab

NOTE Confidence: 0.9723888

00:49:40.025 --> 00:49:41.065 is now a little bit

NOTE Confidence: 0.9723888

00:49:41.065 --> 00:49:41.545 more,

NOTE Confidence: 0.8765956

00:49:42.905 --> 00:49:44.105 it's growing at a in

NOTE Confidence: 0.8765956

00:49:44.105 --> 00:49:45.724 a, at a pace,

NOTE Confidence: 0.9089722

00:49:46.310 --> 00:49:47.510 where I have a a

NOTE Confidence: 0.9089722

00:49:47.510 --> 00:49:49.030 graduate student, a postdoc, I

NOTE Confidence: 0.9089722

00:49:49.030 --> 00:49:50.010 have a few undergrads,

NOTE Confidence: 0.97104675

00:49:50.790 --> 00:49:51.989 which is all very exciting

NOTE Confidence: 0.97104675

00:49:51.989 --> 00:49:53.110 and sort of expanding the

NOTE Confidence: 0.97104675

00:49:53.110 --> 00:49:54.550 scope of our science. I'd

NOTE Confidence: 0.97104675

00:49:54.550 --> 00:49:55.270 like to thank a few

NOTE Confidence: 0.97104675

00:49:55.270 --> 00:49:56.070 of the people that have

NOTE Confidence: 0.97104675

00:49:56.070 --> 00:49:56.630 helped me,

NOTE Confidence: 0.87689674

00:49:57.190 --> 00:49:58.230 perform some of this work,

NOTE Confidence: 0.87689674

00:49:58.230 --> 00:49:59.930 Alex Proick, Max Tells,

NOTE Confidence: 0.99490535

00:50:00.310 --> 00:50:01.130 Tom Joseph,

NOTE Confidence: 0.8845061

00:50:02.835 --> 00:50:04.275 and Andy at Penn. And

NOTE Confidence: 0.8845061

00:50:04.275 --> 00:50:05.475 a special thanks to Lauren

NOTE Confidence: 0.8845061

00:50:05.475 --> 00:50:06.435 Lugar who's been a a

NOTE Confidence: 0.8845061

00:50:06.435 --> 00:50:06.935 close

NOTE Confidence: 0.9763139

00:50:07.315 --> 00:50:08.395 colleague and mentor,

NOTE Confidence: 0.98883504

00:50:08.835 --> 00:50:09.815 since my PhD,

NOTE Confidence: 0.84676504

00:50:10.755 --> 00:50:11.735 and and Kahlal,

NOTE Confidence: 0.910109

00:50:13.555 --> 00:50:15.635 for for, his extraordinary work

NOTE Confidence: 0.910109

00:50:15.635 --> 00:50:16.535 with that ketamine

NOTE Confidence: 0.878004

00:50:17.340 --> 00:50:17.840 sensor,

NOTE Confidence: 0.60872054

00:50:18.780 --> 00:50:19.920 fantastic science,

NOTE Confidence: 0.9613928

00:50:20.300 --> 00:50:21.660 scientist who's, I believe, on

NOTE Confidence: 0.9613928

00:50:21.660 --> 00:50:22.880 the job market now,

NOTE Confidence: 0.9358845

00:50:23.739 --> 00:50:25.340 and Chuck Saromski for helping

NOTE Confidence: 0.9358845

00:50:25.340 --> 00:50:26.220 out with some of the,

NOTE Confidence: 0.9358845

00:50:26.460 --> 00:50:28.380 brain slice recordings and to

NOTE Confidence: 0.9358845

00:50:28.380 --> 00:50:29.900 Peter Nagley who drew me

NOTE Confidence: 0.9358845

00:50:29.900 --> 00:50:30.960 to nitrous oxide,

NOTE Confidence: 0.999313

00:50:31.635 --> 00:50:33.255 when I was previously infatuated

NOTE Confidence: 0.999313

00:50:33.395 --> 00:50:34.135 with ketamine.

NOTE Confidence: 0.973624

00:50:34.915 --> 00:50:35.895 And and lastly,

NOTE Confidence: 0.9996129

00:50:36.515 --> 00:50:37.735 since I have your attention,

NOTE Confidence: 0.9671094

00:50:38.515 --> 00:50:39.235 I just wanna,

NOTE Confidence: 0.9398406

00:50:40.035 --> 00:50:41.315 do a a a plug

NOTE Confidence: 0.9398406

00:50:41.315 --> 00:50:42.695 here for a colleague,

NOTE Confidence: 0.9161611

00:50:43.235 --> 00:50:44.055 who's running,

NOTE Confidence: 0.9989635

00:50:44.594 --> 00:50:45.415 or chairing

NOTE Confidence: 0.9454978

00:50:45.880 --> 00:50:47.560 a fantastic Gordon conference that's

NOTE Confidence: 0.9454978

00:50:47.560 --> 00:50:48.520 gonna be held in in

NOTE Confidence: 0.9454978

00:50:48.520 --> 00:50:50.119 Texas this year, previously in

NOTE Confidence: 0.9454978

00:50:50.119 --> 00:50:52.280 Italy, that is really sort

NOTE Confidence: 0.9454978

00:50:52.280 --> 00:50:53.719 of bridging the gap between

NOTE Confidence: 0.9454978

00:50:53.719 --> 00:50:54.700 conscious neuroscience,

NOTE Confidence: 0.9971011

00:50:55.880 --> 00:50:56.380 anesthesia,

NOTE Confidence: 0.9917531

00:50:56.760 --> 00:50:57.980 psychedelic science,

NOTE Confidence: 0.9287494

00:51:00.224 --> 00:51:01.424 I mean, sleep science.

NOTE Confidence: 0.996598

00:51:01.744 --> 00:51:03.025 So it's bringing together a

NOTE Confidence: 0.996598

00:51:03.025 --> 00:51:04.864 lot of extraordinary people who

NOTE Confidence: 0.996598

00:51:04.864 --> 00:51:06.464 are interested in in sort

NOTE Confidence: 0.996598

00:51:06.464 --> 00:51:07.924 of similar questions,

NOTE Confidence: 0.993837

00:51:08.464 --> 00:51:09.924 maybe using different approaches.

NOTE Confidence: 0.98446274

00:51:10.305 --> 00:51:11.585 It's a great venue. So

NOTE Confidence: 0.98446274

00:51:11.585 --> 00:51:12.805 if you have any interest,

NOTE Confidence: 0.9661089

00:51:13.539 --> 00:51:14.339 in any of this, I

NOTE Confidence: 0.9661089

00:51:14.339 --> 00:51:15.779 would highly suggest you attend

NOTE Confidence: 0.9661089

00:51:15.779 --> 00:51:17.059 just given you can trial

NOTE Confidence: 0.9661089

00:51:17.059 --> 00:51:18.019 it because it's gonna be

NOTE Confidence: 0.9661089

00:51:18.019 --> 00:51:18.900 in the States and a

NOTE Confidence: 0.9661089

00:51:18.900 --> 00:51:20.180 little bit more approachable than

NOTE Confidence: 0.9661089

00:51:20.180 --> 00:51:21.000 going to Italy,

NOTE Confidence: 0.86341864

00:51:21.460 --> 00:51:22.420 which I think is gonna

NOTE Confidence: 0.86341864

00:51:22.420 --> 00:51:23.160 be the same.

NOTE Confidence: 0.9759192

00:51:24.215 --> 00:51:25.175 So thank you so much

NOTE Confidence: 0.9759192

00:51:25.175 --> 00:51:26.215 for your attention. I'm I'm

NOTE Confidence: 0.9759192

00:51:26.215 --> 00:51:27.435 happy to address any,

NOTE Confidence: 0.9507011

00:51:28.135 --> 00:51:28.635 questions.