

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 isoflurine, 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 isoflurine

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.