WEBVTT

00:00:00.000 --> 00:00:03.955 Uhm? First, at as you've probably gathered,

00:00:03.960 --> 00:00:05.860 it's tremendous pleasure to

00:00:05.860 --> 00:00:07.492 welcome our our speaker,

00:00:07.492 --> 00:00:09.436 who will be introduced by somebody

00:00:09.436 --> 00:00:11.219 else but Brian and I go back.

00:00:11.220 --> 00:00:15.240 I think, to residency days and.

00:00:15.240 --> 00:00:17.368 And it's great to have you here today.

00:00:17.370 --> 00:00:19.694 Today we're going to be celebrating the

00:00:19.694 --> 00:00:21.920 the annual George K Agajanian lecture.

00:00:21.920 --> 00:00:26.246 Here is George hard at work.

00:00:26.250 --> 00:00:30.258 In earlier days. This is George.

00:00:30.258 --> 00:00:32.279 It's the early earliest picture that

00:00:32.279 --> 00:00:34.880 I have which is a picture of George in

00:00:34.880 --> 00:00:37.466 1971 and with the department faculty.

NOTE Confidence: 0.967818412857143

00:00:37.470 --> 00:00:39.788 He was born in Beirut, Lebanon.

NOTE Confidence: 0.967818412857143

00:00:39.788 --> 00:00:41.636 He went to college and Cornell.

NOTE Confidence: 0.967818412857143

00:00:41.640 --> 00:00:44.106 He graduated from Yale Medical School

NOTE Confidence: 0.967818412857143

00:00:44.106 --> 00:00:48.310 in 1958 and attended the residency.

NOTE Confidence: 0.967818412857143

00:00:48.310 --> 00:00:53.228 He was in EU S Army core and then rose

NOTE Confidence: 0.967818412857143

00:00:53.228 --> 00:00:56.324 the ranks of Yale faculty becoming

NOTE Confidence: 0.967818412857143

00:00:56.324 --> 00:00:58.790 the foundation's fund professor

NOTE Confidence: 0.967818412857143

00:00:58.790 --> 00:01:01.390 and ultimately professor emeritus.

NOTE Confidence: 0.967818412857143

00:01:01.390 --> 00:01:03.707 If you look closely at this picture,

NOTE Confidence: 0.967818412857143

00:01:03.710 --> 00:01:05.490 you see not only George,

NOTE Confidence: 0.967818412857143

00:01:05.490 --> 00:01:08.262 but you also see George Henninger John

NOTE Confidence: 0.967818412857143

00:01:08.262 --> 00:01:11.550 Flynn for whom the Flynn lecture is named.

NOTE Confidence: 0.967818412857143

00:01:11.550 --> 00:01:13.452 And of course,

NOTE Confidence: 0.967818412857143

00:01:13.452 --> 00:01:17.256 Steve Bunny and George and Steve.

NOTE Confidence: 0.967818412857143

00:01:17.260 --> 00:01:19.070 George Heneghan Stevonnie are also

NOTE Confidence: 0.967818412857143

00:01:19.070 --> 00:01:23.130 with us today, so it's a it's great.

NOTE Confidence: 0.967818412857143

00:01:23.130 --> 00:01:25.310 So in in medical school,

NOTE Confidence: 0.967818412857143

00:01:25.310 --> 00:01:29.538 George became connected to a

NOTE Confidence: 0.967818412857143

00:01:29.538 --> 00:01:32.698 mentee of Daniel X Friedman,

NOTE Confidence: 0.967818412857143

00:01:32.700 --> 00:01:34.602 charismatic, trailblazing,

NOTE Confidence: 0.967818412857143

00:01:34.602 --> 00:01:38.406 innovator in biological psychiatry,

NOTE Confidence: 0.967818412857143

00:01:38.410 --> 00:01:40.996 who led the Biological psychiatry group

NOTE Confidence: 0.967818412857143

00:01:40.996 --> 00:01:44.343 at Yale from the 50s until he left in

NOTE Confidence: 0.967818412857143

00:01:44.343 --> 00:01:46.702 the mid 60s and George's first paper.

NOTE Confidence: 0.967818412857143

00:01:46.702 --> 00:01:48.850 As far as I can tell,

NOTE Confidence: 0.967818412857143

00:01:48.850 --> 00:01:51.178 was on the topic of related to the

NOTE Confidence: 0.967818412857143

00:01:51.178 --> 00:01:54.094 topic of our lecture today, which is.

NOTE Confidence: 0.967818412857143

00:01:54.094 --> 00:01:56.704 The actions of psychedelic drugs,

NOTE Confidence: 0.967818412857143

00:01:56.710 --> 00:01:59.923 which this is when he was a medical student,

NOTE Confidence: 0.967818412857143

00:01:59.930 --> 00:02:02.135 his first medical school medical

NOTE Confidence: 0.967818412857143

00:02:02.135 --> 00:02:04.248 student paper, of course,

NOTE Confidence: 0.967818412857143

00:02:04.248 --> 00:02:06.090 appeared in science.

NOTE Confidence: 0.967818412857143

00:02:06.090 --> 00:02:06.596 Uhm,

NOTE Confidence: 0.967818412857143

00:02:06.596 --> 00:02:09.416 and and George pursued the psychedelic

NOTE Confidence: 0.967818412857143

00:02:09.416 --> 00:02:11.924 drugs throughout his career as a

NOTE Confidence: 0.967818412857143

00:02:11.924 --> 00:02:15.615 Reece area of research in in 1968.

NOTE Confidence: 0.967818412857143

00:02:15.615 --> 00:02:19.272 He recorded the effects of psychedelic

NOTE Confidence: 0.967818412857143

00:02:19.272 --> 00:02:23.220 drugs on the activity of serotonin neurons.

NOTE Confidence: 0.967818412857143

00:02:23.220 --> 00:02:25.908 I suspect he was the first scientist to

NOTE Confidence: 0.967818412857143

00:02:25.908 --> 00:02:28.667 record the activity of serotonin neurons,

NOTE Confidence: 0.967818412857143

00:02:28.670 --> 00:02:32.500 and he said one explanation for this

NOTE Confidence: 0.967818412857143

00:02:32.500 --> 00:02:34.700 common behavioral effect of LSD.

NOTE Confidence: 0.967818412857143

00:02:34.700 --> 00:02:35.846 In addition.

NOTE Confidence: 0.967818412857143

00:02:35.846 --> 00:02:38.138 Two suppressing raffey activity

NOTE Confidence: 0.967818412857143

00:02:38.138 --> 00:02:41.568 was that LSD acted like serotonin

NOTE Confidence: 0.967818412857143

00:02:41.568 --> 00:02:44.661 at a postsynaptic site in 1968.

NOTE Confidence: 0.967818412857143

00:02:44.661 --> 00:02:47.607 That postsynaptic site was not clear,

NOTE Confidence: 0.967818412857143

00:02:47.610 --> 00:02:53.258 but in 1979, as he continued to study it,

NOTE Confidence: 0.967818412857143

00:02:53.260 --> 00:02:56.329 which just happens to be the same year that,

NOTE Confidence: 0.967818412857143

00:02:56.330 --> 00:02:57.378 through reset.

NOTE Confidence: 0.967818412857143

00:02:57.378 --> 00:02:58.950 Radio receptor assays,

NOTE Confidence: 0.967818412857143

00:02:58.950 --> 00:03:00.684 the serotonin receptor,

NOTE Confidence: 0.967818412857143

00:03:00.684 --> 00:03:02.996 serotonin 2 receptors identified

NOTE Confidence: 0.967818412857143

00:03:03.000 --> 00:03:05.164 was that physiologically using

NOTE Confidence: 0.967818412857143

00:03:05.164 --> 00:03:06.787 facial motor neuron.

NOTE Confidence: 0.967818412857143

00:03:06.790 --> 00:03:09.234 Citation he using Physiology,

NOTE Confidence: 0.967818412857143

00:03:09.234 --> 00:03:12.900 found a second site for serotonin

NOTE Confidence: 0.967818412857143

00:03:13.003 --> 00:03:14.764 that was facilitated excitatory

NOTE Confidence: 0.967818412857143

00:03:14.764 --> 00:03:17.716 inputs and was blocked by methyl

NOTE Confidence: 0.967818412857143

00:03:17.716 --> 00:03:19.940 surgilight which we would of course

NOTE Confidence: 0.967818412857143

00:03:19.940 --> 00:03:22.400 now call a serotonin 2A receptor.

NOTE Confidence: 0.9909622

00:03:25.050 --> 00:03:28.390 But George was not only a uh,

NOTE Confidence: 0.9909622

00:03:28.390 --> 00:03:31.890 a, uh? Involved in.

NOTE Confidence: 0.9918363

00:03:33.930 --> 00:03:36.125 Serotonin neurons he mentored

NOTE Confidence: 0.9918363

00:03:36.125 --> 00:03:39.590 Steve Bunny and they were the first

NOTE Confidence: 0.9918363

00:03:39.590 --> 00:03:43.979 to record from dopamine neurons.

NOTE Confidence: 0.9918363

00:03:43.979 --> 00:03:47.657 And here is Steve and George

NOTE Confidence: 0.9918363

00:03:47.657 --> 00:03:50.322 together playing with the amplifiers.

NOTE Confidence: 0.9918363

00:03:50.322 --> 00:03:52.887 Obviously doing something with with

NOTE Confidence: 0.9918363

00:03:52.887 --> 00:03:55.826 their with their rig there in the lab.

NOTE Confidence: 0.9918363

00:03:55.830 --> 00:04:01.530 Uhm and then came, uhm, uh? Uh.

NOTE Confidence: 0.9918363

00:04:01.530 --> 00:04:05.040 Another Seminole paper, this time

NOTE Confidence: 0.986224325

00:04:05.760 --> 00:04:07.518 one of the first studies may be the

NOTE Confidence: 0.986224325

00:04:07.518 --> 00:04:09.618 first study to record from Norwich

NOTE Confidence: 0.94547220375

00:04:09.630 --> 00:04:12.734 in Ergic neurons in the locus through list,

NOTE Confidence: 0.94547220375

00:04:12.740 --> 00:04:15.158 and this was an incredibly Seminole

NOTE Confidence: 0.94547220375

00:04:15.158 --> 00:04:17.982 study where he showed that morphine

NOTE Confidence: 0.94547220375

00:04:17.982 --> 00:04:21.016 suppressed the locus release but also a

NOTE Confidence: 0.94547220375

00:04:21.016 --> 00:04:23.746 spare tone and agonist Clonidine could

NOTE Confidence: 0.94547220375

00:04:23.746 --> 00:04:26.746 suppress locus neurons that are activated

NOTE Confidence: 0.94547220375

00:04:26.746 --> 00:04:30.090 as a result of opiate withdrawal.

NOTE Confidence: 0.94547220375

00:04:30.090 --> 00:04:31.686 So you could suppress.

NOTE Confidence: 0.94547220375

00:04:31.686 --> 00:04:33.282 Opiate withdrawal related activation

NOTE Confidence: 0.94547220375

00:04:33.282 --> 00:04:35.892 of the locust with morphine or with

NOTE Confidence: 0.94547220375

00:04:35.892 --> 00:04:39.600 the non opiate Clonidine and this

NOTE Confidence: 0.94547220375

00:04:39.600 --> 00:04:42.993 led to the first rational testing.

NOTE Confidence: 0.94547220375

00:04:42.993 --> 00:04:46.080 If you will mechanistic testing of a

NOTE Confidence: 0.94547220375

00:04:46.157 --> 00:04:49.349 drug in psychiatry as a treatment which

NOTE Confidence: 0.94547220375

00:04:49.349 --> 00:04:51.710 was the identification of Clonidine

NOTE Confidence: 0.94547220375

00:04:51.710 --> 00:04:54.464 as a treatment for opiate withdrawal.

NOTE Confidence: 0.94547220375

00:04:54.470 --> 00:04:57.858 When I say rationally mean whether a

NOTE Confidence: 0.94547220375

00:04:57.858 --> 00:05:00.430 specific signaling mechanism was high.

NOTE Confidence: 0.94547220375

00:05:00.430 --> 00:05:01.438 Related hypothesis.

NOTE Confidence: 0.94547220375

00:05:01.438 --> 00:05:05.090 Was tested and this study appeared in 78.

NOTE Confidence: 0.94547220375

00:05:05.090 --> 00:05:07.226 We actually was a huge inspiration

NOTE Confidence: 0.94547220375

00:05:07.226 --> 00:05:10.041 to me and and one of the reasons

NOTE Confidence: 0.94547220375

00:05:10.041 --> 00:05:12.450 that I ended up coming to Yale.

NOTE Confidence: 0.94547220375

00:05:12.450 --> 00:05:16.246 But George has been an innovator

NOTE Confidence: 0.94547220375

00:05:16.246 --> 00:05:20.058 throughout his career and in some

NOTE Confidence: 0.94547220375

00:05:20.058 --> 00:05:24.286 ways his critical role in establishing

NOTE Confidence: 0.94547220375

00:05:24.286 --> 00:05:26.698 mechanisms associated with rapid

NOTE Confidence: 0.94547220375

00:05:26.698 --> 00:05:29.500 antidepressant effects of CADA mean

NOTE Confidence: 0.94547220375

00:05:29.500 --> 00:05:32.640 in the Seminole Science paper from

NOTE Confidence: 0.94547220375

00:05:32.640 --> 00:05:36.840 George and and the late Run Doom,

NOTE Confidence: 0.94547220375

00:05:36.840 --> 00:05:40.855 and who we who we all miss a great deal and.

NOTE Confidence: 0.94547220375

00:05:40.855 --> 00:05:42.630 And we had the pleasure.

NOTE Confidence: 0.94547220375

00:05:42.630 --> 00:05:44.914 Of celebrating Georges career.

NOTE Confidence: 0.94547220375

00:05:44.914 --> 00:05:50.490 In fact, the two Georges in 2014.

NOTE Confidence: 0.94547220375

00:05:50.490 --> 00:05:54.788 And this was the speakers from that from

NOTE Confidence: 0.94547220375

00:05:54.788 --> 00:05:58.304 that invitation in that that celebration,

NOTE Confidence: 0.94547220375

00:05:58.310 --> 00:05:59.770 I would have to say,

NOTE Confidence: 0.94547220375

00:05:59.770 --> 00:06:01.650 looking back on that you

NOTE Confidence: 0.94547220375

00:06:01.650 --> 00:06:03.801 you might legitimately ask,

NOTE Confidence: 0.94547220375

00:06:03.801 --> 00:06:07.840 where's the diversity here in this list?

NOTE Confidence: 0.94547220375

00:06:07.840 --> 00:06:10.864 And I think hindsight is really important.

NOTE Confidence: 0.94547220375

00:06:10.870 --> 00:06:13.768 It probably would have a different,

NOTE Confidence: 0.94547220375

00:06:13.770 --> 00:06:15.020 somewhat different group if we

NOTE Confidence: 0.94547220375

00:06:15.020 --> 00:06:16.270 were to do it again.

NOTE Confidence: 0.94547220375

00:06:16.270 --> 00:06:20.572 So but this is this is a wonderful day.

NOTE Confidence: 0.94547220375

00:06:20.580 --> 00:06:24.196 A great group of speakers and great to

NOTE Confidence: 0.94547220375

00:06:24.196 --> 00:06:27.726 be together with everybody at that time.

NOTE Confidence: 0.94547220375

00:06:27.730 --> 00:06:30.484 I just want to highlight that that

NOTE Confidence: 0.94547220375

00:06:30.484 --> 00:06:33.403 George is not only a Seminole scientist,

NOTE Confidence: 0.94547220375

00:06:33.410 --> 00:06:38.180 but also an incredibly important collaborator

NOTE Confidence: 0.94547220375

00:06:38.180 --> 00:06:41.120 and mentor and important to many,

NOTE Confidence: 0.94547220375

00:06:41.120 --> 00:06:44.020 many careers, including my own.

NOTE Confidence: 0.94547220375

00:06:44.020 --> 00:06:44.341 Uhm,

NOTE Confidence: 0.94547220375

00:06:44.341 --> 00:06:46.909 and of course he won many many honors,

NOTE Confidence: 0.94547220375

00:06:46.910 --> 00:06:48.480 including the Lieber Prize from

NOTE Confidence: 0.94547220375

00:06:48.480 --> 00:06:50.828 NARSAD is a member of the Institute

NOTE Confidence: 0.94547220375

00:06:50.828 --> 00:06:52.964 of Medicine and received the Axelrod

NOTE Confidence: 0.94547220375

00:06:52.964 --> 00:06:55.277 Award for mentorship from the AC NP.

NOTE Confidence: 0.94547220375

00:06:55.280 --> 00:06:58.210 So a brief run through

NOTE Confidence: 0.932298316666667

00:07:00.450 --> 00:07:04.140 A RR career of George George.

NOTE Confidence: 0.932298316666667

00:07:04.140 --> 00:07:06.380 I didn't see whether you're on the line.

NOTE Confidence: 0.932298316666667

00:07:06.380 --> 00:07:08.998 I'm assuming you are and just say,

NOTE Confidence: 0.932298316666667

00:07:09.000 --> 00:07:11.807 once again, how deeply we appreciate all

NOTE Confidence: 0.932298316666667

00:07:11.807 --> 00:07:14.218 that you've brought to us individually and.

NOTE Confidence: 0.932298316666667

00:07:14.218 --> 00:07:17.160 US as an apartment and we're thrilled to have

NOTE Confidence: 0.932298316666667

00:07:17.160 --> 00:07:19.290 a lecture to celebrate your contributions

NOTE Confidence: 0.932298316666667

00:07:19.290 --> 00:07:21.449 to science and to the department.

NOTE Confidence: 0.932298316666667

00:07:21.450 --> 00:07:25.920 So I'll I'll stop it at that point and and

NOTE Confidence: 0.932298316666667

00:07:26.034 --> 00:07:29.360 pass it on to others who are continuing.

NOTE Confidence: 0.932298316666667

00:07:29.360 --> 00:07:31.200 The introduction. Marina thanks.

NOTE Confidence: 0.8745166

00:07:33.890 --> 00:07:36.268 Well, thank you for starting

NOTE Confidence: 0.8745166

00:07:36.268 --> 00:07:39.940 us off John. I won't

NOTE Confidence: 0.9894603025

00:07:39.940 --> 00:07:42.369 share my screen because I think all

NOTE Confidence: 0.9894603025

00:07:42.369 --> 00:07:44.826 of us have now seen Dr Agajanian's

NOTE Confidence: 0.9894603025

00:07:44.826 --> 00:07:47.770 photo and I know you'll see it again.

NOTE Confidence: 0.9894603025

00:07:47.770 --> 00:07:50.965 So I want to start by introducing Dr Roth.

NOTE Confidence: 0.9894603025

00:07:50.970 --> 00:07:54.126 Thank you for being with us.

NOTE Confidence: 0.9894603025

00:07:54.130 --> 00:07:55.192 Quick background doctor.

NOTE Confidence: 0.9894603025

00:07:55.192 --> 00:07:56.636 Roth received his undergraduate

NOTE Confidence: 0.9894603025

00:07:56.636 --> 00:07:57.719 degree in Biology,

NOTE Confidence: 0.9894603025

00:07:57.720 --> 00:08:00.289 Biology and chemistry and then his MD,

NOTE Confidence: 0.9894603025

00:08:00.290 --> 00:08:03.422 PhD before he went on to work at the

NOTE Confidence: 0.9894603025

00:08:03.422 --> 00:08:06.650 NIH Lab of Preclinical Pharmacology,

NOTE Confidence: 0.9894603025

00:08:06.650 --> 00:08:09.898 and he then went back and completed his

NOTE Confidence: 0.9894603025

00:08:09.898 --> 00:08:13.320 residency in psychiatry at Stanford and then

NOTE Confidence: 0.9894603025

00:08:13.320 --> 00:08:16.155 after 15 years at Case Western Reserve,

NOTE Confidence: 0.9894603025

00:08:16.160 --> 00:08:18.256 he moved to UNC Chapel Hill in 2006,

NOTE Confidence: 0.9894603025

00:08:18.260 --> 00:08:20.708 and he's currently the Michael ******

NOTE Confidence: 0.9894603025

00:08:20.710 --> 00:08:22.922 Distinguished professor of Protein

NOTE Confidence: 0.9894603025

00:08:22.922 --> 00:08:25.134 Therapeutics and Translational Proteomics.

NOTE Confidence: 0.9894603025

00:08:25.140 --> 00:08:26.340 In the Department of Pharmacology,

NOTE Confidence: 0.9894603025

00:08:26.340 --> 00:08:28.536 and I must say that is the most specific

NOTE Confidence: 0.9894603025

00:08:28.536 --> 00:08:30.266 named chair that I've ever heard.

NOTE Confidence: 0.9894603025

00:08:30.270 --> 00:08:32.206 I really like that.

NOTE Confidence: 0.9894603025

00:08:32.206 --> 00:08:34.802 Uhm, he has joint appointments also in

NOTE Confidence: 0.9894603025

00:08:34.802 --> 00:08:36.820 chemical biology and medicinal chemistry,

NOTE Confidence: 0.9894603025

00:08:36.820 --> 00:08:38.610 which really shows how important

NOTE Confidence: 0.9894603025

00:08:38.610 --> 00:08:40.885 his basic work is to translation

NOTE Confidence: 0.9894603025

00:08:40.885 --> 00:08:42.965 into treatment and he is.

NOTE Confidence: 0.9894603025

00:08:42.970 --> 00:08:44.559 This has been a theme of his

NOTE Confidence: 0.9894603025

00:08:44.559 --> 00:08:45.620 work throughout his career.

NOTE Confidence: 0.9894603025

00:08:45.620 --> 00:08:48.217 He's really pushed the boundaries of how

NOTE Confidence: 0.9894603025

00:08:48.217 --> 00:08:50.960 we look at the structure of G protein,

NOTE Confidence: 0.9894603025

00:08:50.960 --> 00:08:52.480 protein coupled receptors and

NOTE Confidence: 0.9894603025

00:08:52.480 --> 00:08:54.000 tie that to function.

NOTE Confidence: 0.9894603025

00:08:54.000 --> 00:08:56.900 And he's also been incredibly

NOTE Confidence: 0.9894603025

00:08:56.900 --> 00:08:59.220 influential and molecular pharmacology

NOTE Confidence: 0.9894603025

00:08:59.220 --> 00:09:01.740 and synthetic neurobiology.

NOTE Confidence: 0.9894603025

00:09:01.740 --> 00:09:03.995 He is really committed to

NOTE Confidence: 0.9894603025

00:09:03.995 --> 00:09:06.250 the open sharing of reagents,

NOTE Confidence: 0.9894603025

00:09:06.250 --> 00:09:08.273 and I think this is one of

NOTE Confidence: 0.9894603025

00:09:08.273 --> 00:09:09.820 the hallmarks of his work.

NOTE Confidence: 0.9894603025

00:09:09.820 --> 00:09:11.788 We've benefited from his reagents as

NOTE Confidence: 0.9894603025

00:09:11.788 --> 00:09:13.962 have probably most most people in the

NOTE Confidence: 0.9894603025

00:09:13.962 --> 00:09:15.838 field that are related to his work,

NOTE Confidence: 0.9894603025

00:09:15.840 --> 00:09:17.790 because there have been more

NOTE Confidence: 0.9894603025

00:09:17.790 --> 00:09:20.660 than 32,000 orders,

NOTE Confidence: 0.9894603025

00:09:20.660 --> 00:09:22.766 probably more by now from Addgene

NOTE Confidence: 0.9894603025

00:09:22.766 --> 00:09:25.210 that have gone to the scientific

NOTE Confidence: 0.9894603025

00:09:25.210 --> 00:09:28.175 community to further to further the

NOTE Confidence: 0.9894603025

00:09:28.175 --> 00:09:31.205 translational work that he is done.

NOTE Confidence: 0.9894603025

00:09:31.210 --> 00:09:33.898 Doctor Roth was elected to the National

NOTE Confidence: 0.9894603025

00:09:33.898 --> 00:09:36.180 Academy of Medicine and to the

NOTE Confidence: 0.9894603025

00:09:36.180 --> 00:09:38.304 American Academy of Arts and Sciences.

NOTE Confidence: 0.9894603025

00:09:38.310 --> 00:09:39.285 He's been named,

NOTE Confidence: 0.9894603025

00:09:39.285 --> 00:09:40.260 which I love.

NOTE Confidence: 0.9894603025

00:09:40.260 --> 00:09:43.032 This one of the world's most influential

00:09:43.032 --> 00:09:45.075 scientific minds by Thomson Reuters.

00:09:45.075 --> 00:09:47.150 And as you've just heard,

00:09:47.150 --> 00:09:49.466 George Aghajanian was a pioneer in

00:09:49.466 --> 00:09:51.710 studying serotonin and its receptors,

00:09:51.710 --> 00:09:53.456 and now Doctor Roth and his

00:09:53.456 --> 00:09:55.194 colleagues have carried out structural

00:09:55.194 --> 00:09:57.270 determinations of serotonin receptors.

00:09:57.270 --> 00:09:57.664 And,

00:09:57.664 --> 00:09:58.452 really excitingly,

00:09:58.452 --> 00:10:00.816 his lab has solved the structures

00:10:00.816 --> 00:10:02.200 of hallucinogens.

00:10:02.200 --> 00:10:04.900 And complex with human serotonin

00:10:04.900 --> 00:10:08.510 receptors and the most recent of that

00:10:08.510 --> 00:10:11.359 came out in 2020 and cell biology.

00:10:11.360 --> 00:10:12.626 In cell biology,

00:10:12.626 --> 00:10:16.660 so we don't need more than one word there.

NOTE Confidence: 0.9894603025

00:10:16.660 --> 00:10:18.655 And really, just from a personal note,

NOTE Confidence: 0.9894603025

00:10:18.660 --> 00:10:21.159 Doctor Ruff is very simply a really

NOTE Confidence: 0.9894603025

00:10:21.159 --> 00:10:23.910 fun person to talk to about science.

NOTE Confidence: 0.9894603025

00:10:23.910 --> 00:10:24.960 He is creative,

NOTE Confidence: 0.9894603025

00:10:24.960 --> 00:10:27.410 he doesn't rest in one area and

NOTE Confidence: 0.9894603025

00:10:27.489 --> 00:10:29.995 that I think that restless mind is

NOTE Confidence: 0.9894603025

00:10:29.995 --> 00:10:32.559 what makes an exciting scientist.

NOTE Confidence: 0.9894603025

00:10:32.560 --> 00:10:34.728 So I hope I hope you'll join me

NOTE Confidence: 0.9894603025

00:10:34.728 --> 00:10:36.751 in welcoming Dr Roth for the

NOTE Confidence: 0.9894603025

00:10:36.751 --> 00:10:37.810 Agajanian Lecture today.

NOTE Confidence: 0.9894603025

00:10:37.810 --> 00:10:40.358 He's an ideal person for this lecture.

NOTE Confidence: 0.9894603025

00:10:40.360 --> 00:10:41.590 Thank you for being with us.

NOTE Confidence: 0.883117127142857

00:10:42.770 --> 00:10:46.165 Thank you, uh, can you hear me?

NOTE Confidence: 0.883117127142857

00:10:46.170 --> 00:10:48.163 Yes yeah OK great.

NOTE Confidence: 0.883117127142857

00:10:48.163 --> 00:10:50.218 Uhm, thank you very much.

NOTE Confidence: 0.883117127142857

00:10:50.220 --> 00:10:53.930 It's a tremendous honor to.

NOTE Confidence: 0.883117127142857

00:10:53.930 --> 00:10:56.930 Give this lecture.

NOTE Confidence: 0.883117127142857

00:10:56.930 --> 00:11:00.918 I know George. Ah.

NOTE Confidence: 0.883117127142857

00:11:00.920 --> 00:11:02.550 You've seen his picture here.

NOTE Confidence: 0.883117127142857

00:11:02.550 --> 00:11:04.974 I just want to say a few things

NOTE Confidence: 0.883117127142857

00:11:04.974 --> 00:11:07.130 about George as a person. Uhm?

NOTE Confidence: 0.9854989425

00:11:09.420 --> 00:11:10.980 Let's see here.

NOTE Confidence: 0.9854989425

00:11:10.980 --> 00:11:13.768 Oh so I think everybody who who

NOTE Confidence: 0.9854989425

00:11:13.768 --> 00:11:15.860 has ever interacted with George.

NOTE Confidence: 0.9854989425

00:11:15.860 --> 00:11:19.416 Knows him as a very kind person.

NOTE Confidence: 0.9854989425

00:11:19.420 --> 00:11:22.507 You can see from his face he has this.

NOTE Confidence: 0.9854989425

00:11:22.510 --> 00:11:25.354 Really open uh expression,

NOTE Confidence: 0.9854989425

00:11:25.354 --> 00:11:29.410 warm and generous, and.

NOTE Confidence: 0.9854989425

00:11:29.410 --> 00:11:33.928 He certainly was that was that way with me.

NOTE Confidence: 0.9854989425

00:11:33.930 --> 00:11:37.618 In everything. The other thing is,

NOTE Confidence: 0.9854989425

00:11:37.618 --> 00:11:39.328 his work is tremendously visionary,

NOTE Confidence: 0.9854989425

00:11:39.330 --> 00:11:41.166 so as as mentioned,

NOTE Confidence: 0.9854989425

00:11:41.166 --> 00:11:44.607 he was one of the very first

NOTE Confidence: 0.9854989425

00:11:44.607 --> 00:11:47.514 people to study psychedelic drugs.

NOTE Confidence: 0.9854989425

00:11:47.514 --> 00:11:50.474 Really, from a mechanistic perspective.

NOTE Confidence: 0.9854989425

00:11:50.480 --> 00:11:54.693 Uhm, and that that continued really,

NOTE Confidence: 0.9854989425

00:11:54.693 --> 00:11:56.772 until until recently,

NOTE Confidence: 0.9854989425

00:11:56.772 --> 00:12:00.237 when his lab shut down.

NOTE Confidence: 0.9854989425

00:12:00.240 --> 00:12:03.150 And as well, the the.

NOTE Confidence: 0.9854989425

00:12:03.150 --> 00:12:06.250 A discovery that John Crystal

NOTE Confidence: 0.9854989425

00:12:06.250 --> 00:12:09.426 highlighted for the use of A2 agonists,

NOTE Confidence: 0.9854989425

00:12:09.430 --> 00:12:11.530 Clonidine for the treatment of

NOTE Confidence: 0.9854989425

00:12:11.530 --> 00:12:12.370 morphine withdrawal.

NOTE Confidence: 0.9854989425

00:12:12.370 --> 00:12:14.434 I agree, really, is.

NOTE Confidence: 0.9854989425

00:12:14.434 --> 00:12:17.990 It's a foundational discovery in the area

NOTE Confidence: 0.9854989425

00:12:17.990 --> 00:12:22.070 of neurosciences and biological psychiatry.

00:12:22.070 --> 00:12:25.724 And when I give lectures on opioids,

00:12:25.730 --> 00:12:28.227 I always present his data because

00:12:28.227 --> 00:12:30.866 it is as far I think think.

00:12:30.870 --> 00:12:33.525 John is right as far as as anyone knows.

00:12:33.530 --> 00:12:36.066 This is this was the first sort of

00:12:36.070 --> 00:12:39.886 mechanistic based treatment for a neuro

00:12:39.886 --> 00:12:43.508 psychiatric disorder and you know amazingly,

00:12:43.508 --> 00:12:45.269 after you know,

00:12:45.270 --> 00:12:47.573 I think probably within days or weeks

00:12:47.573 --> 00:12:50.422 of making the discovery in the lab they

00:12:50.422 --> 00:12:52.240 were already doing studies in patients.

00:12:52.240 --> 00:12:54.240 I think across the hall,

00:12:54.240 --> 00:12:56.950 so it's it's truly amazing.

00:12:56.950 --> 00:13:00.454 And the other thing about George

00:13:00.454 --> 00:13:03.670 that that many people don't know.

00:13:03.670 --> 00:13:04.005 Uh,

NOTE Confidence: 0.9854989425

00:13:04.005 --> 00:13:07.342 is that I think he's an avid golfer and I,

NOTE Confidence: 0.9854989425

00:13:07.342 --> 00:13:07.994 I never.

NOTE Confidence: 0.9854989425

00:13:07.994 --> 00:13:09.950 I never had a chance to

NOTE Confidence: 0.9854989425

00:13:10.038 --> 00:13:11.878 to play golf with him.

NOTE Confidence: 0.9854989425

00:13:11.880 --> 00:13:12.311 Uh,

NOTE Confidence: 0.9854989425

00:13:12.311 --> 00:13:14.897 but my understanding is from people

NOTE Confidence: 0.9854989425

00:13:14.897 --> 00:13:17.424 who have is that he scrutinized

NOTE Confidence: 0.9854989425

00:13:17.424 --> 00:13:20.238 how you played golf before he would

NOTE Confidence: 0.9854989425

00:13:20.238 --> 00:13:22.946 agree to collaborate with you to see.

NOTE Confidence: 0.981378257272727

00:13:25.970 --> 00:13:28.330 To see if to see the sort of person you were,

NOTE Confidence: 0.981378257272727

00:13:28.330 --> 00:13:31.178 he could he sort of used that as

NOTE Confidence: 0.981378257272727

00:13:31.178 --> 00:13:34.689 a as a psychoanalytic technology.

NOTE Confidence: 0.981378257272727

00:13:34.690 --> 00:13:35.887 I told him I didn't play golf,

NOTE Confidence: 0.981378257272727

00:13:35.890 --> 00:13:37.066 'cause I wasn't any good at it,

NOTE Confidence: 0.981378257272727

00:13:37.070 --> 00:13:39.434 so I I don't know what he what

NOTE Confidence: 0.981378257272727

00:13:39.434 --> 00:13:41.554 he gained about my personality

NOTE Confidence: 0.981378257272727

00:13:41.554 --> 00:13:45.860 from that but but that's it. Uhm?

NOTE Confidence: 0.981378257272727

00:13:45.860 --> 00:13:48.948 So what I want to talk about today

NOTE Confidence: 0.981378257272727

00:13:48.948 --> 00:13:52.364 is our our recent studies from my

NOTE Confidence: 0.981378257272727

00:13:52.364 --> 00:13:55.130 lab on psychedelic drug action.

NOTE Confidence: 0.981378257272727

00:13:55.130 --> 00:13:58.140 And before I start just a few

NOTE Confidence: 0.981378257272727

00:13:58.140 --> 00:14:01.180 disclosures as as was mentioned already,

NOTE Confidence: 0.981378257272727

00:14:01.180 --> 00:14:04.078 everything from the lab that we

NOTE Confidence: 0.981378257272727

00:14:04.078 --> 00:14:06.610 develop is available from aging.

NOTE Confidence: 0.981378257272727

00:14:06.610 --> 00:14:09.668 All the work reported here today is

NOTE Confidence: 0.981378257272727

00:14:09.668 --> 00:14:13.154 supported by the NIH or by DARPA.

NOTE Confidence: 0.981378257272727

00:14:13.160 --> 00:14:15.672 Uhm? Just one note,

NOTE Confidence: 0.981378257272727

00:14:15.672 --> 00:14:19.108 I may reveal some compounds toward

NOTE Confidence: 0.981378257272727

00:14:19.108 --> 00:14:21.260 the end of the lecture and a

NOTE Confidence: 0.981378257272727

00:14:21.260 --> 00:14:23.390 patent has been submitted by Yale

NOTE Confidence: 0.981378257272727

00:14:23.390 --> 00:14:25.229 University for these compounds.

NOTE Confidence: 0.981378257272727

00:14:25.230 --> 00:14:28.860 So Bill, Yale and you can follow

NOTE Confidence: 0.981378257272727

00:14:28.860 --> 00:14:32.660 me on Twitter if you wish.

NOTE Confidence: 0.981378257272727

00:14:32.660 --> 00:14:33.374 I don't know.

NOTE Confidence: 0.981378257272727

00:14:33.374 --> 00:14:35.779 I'd ask you not to share the data slides.

NOTE Confidence: 0.981378257272727

00:14:35.780 --> 00:14:39.770 Because some of this is unpublished work.

NOTE Confidence: 0.981378257272727

00:14:39.770 --> 00:14:41.744 So what I'm going to do today

NOTE Confidence: 0.981378257272727

00:14:41.744 --> 00:14:43.510 is talk about psychedelics.

NOTE Confidence: 0.981378257272727

00:14:43.510 --> 00:14:46.390 And psychedelic drugs of course,

NOTE Confidence: 0.981378257272727

00:14:46.390 --> 00:14:47.932 have a long,

NOTE Confidence: 0.981378257272727

00:14:47.932 --> 00:14:50.502 long history going back to

NOTE Confidence: 0.981378257272727

00:14:50.502 --> 00:14:53.720 the pre Christian era when.

NOTE Confidence: 0.981378257272727

00:14:53.720 --> 00:14:56.900 Psychedelic plants like low for a

NOTE Confidence: 0.981378257272727

00:14:56.900 --> 00:15:02.580 Willie MC AKA Payodhi tactas thus.

NOTE Confidence: 0.981378257272727

00:15:02.580 --> 00:15:06.006 Plant that makes mescalin and the

NOTE Confidence: 0.981378257272727

00:15:06.006 --> 00:15:09.086 fungus psylocybe mexicana which makes

NOTE Confidence: 0.981378257272727

00:15:09.086 --> 00:15:14.620 psilocybin were widely used, particularly in.

NOTE Confidence: 0.981378257272727

00:15:14.620 --> 00:15:17.038 In the Americas.

NOTE Confidence: 0.981378257272727

00:15:17.040 --> 00:15:18.820 And.

NOTE Confidence: 0.981378257272727

00:15:18.820 --> 00:15:21.500 More recently.

NOTE Confidence: 0.981378257272727

00:15:21.500 --> 00:15:24.550 Following the discovery of LSD

NOTE Confidence: 0.981378257272727

00:15:24.550 --> 00:15:27.250 by Albert Hofmann in 1943,

NOTE Confidence: 0.981378257272727

00:15:27.250 --> 00:15:31.010 there was really a resurgence in interest

NOTE Confidence: 0.981378257272727

00:15:31.010 --> 00:15:34.126 in psychedelics as drugs initially,

NOTE Confidence: 0.981378257272727

00:15:34.126 --> 00:15:36.262 because it was thought that drugs

NOTE Confidence: 0.981378257272727

00:15:36.262 --> 00:15:38.999 like LSD induced a sort of model

NOTE Confidence: 0.981378257272727

00:15:38.999 --> 00:15:40.603 psychosis schizophrenia like condition.

NOTE Confidence: 0.981378257272727

00:15:40.610 --> 00:15:41.214 Of course,

NOTE Confidence: 0.981378257272727

00:15:41.214 --> 00:15:43.026 we don't think that's true anymore,

NOTE Confidence: 0.981378257272727

00:15:43.030 --> 00:15:46.838 but it it inspired a lot of research.

NOTE Confidence: 0.981378257272727

00:15:46.840 --> 00:15:48.600 And in the 1960s,

NOTE Confidence: 0.981378257272727

00:15:48.600 --> 00:15:50.800 a number of mescaline analogs

NOTE Confidence: 0.981378257272727

00:15:50.800 --> 00:15:52.350 were synthesized.

NOTE Confidence: 0.97775244

00:15:54.700 --> 00:15:57.928 By Sheldon and others and his,

NOTE Confidence: 0.97775244

00:15:57.930 --> 00:16:00.610 uh, his first person accounts

NOTE Confidence: 0.97775244

00:16:00.610 --> 00:16:03.010 are celebrated now in two books,

NOTE Confidence: 0.97775244

00:16:03.010 --> 00:16:05.980 pycal and fennel isopropylamine's.

NOTE Confidence: 0.97775244

00:16:05.980 --> 00:16:07.430 I have known and loved

NOTE Confidence: 0.97775244

00:16:07.430 --> 00:16:08.722 and Tikal on tryptamines.

NOTE Confidence: 0.97775244

00:16:08.722 --> 00:16:10.337 I have known and loved.

NOTE Confidence: 0.986912882

00:16:12.440 --> 00:16:15.200 In in the early 1960s,

NOTE Confidence: 0.986912882

00:16:15.200 --> 00:16:17.550 biological assays that were or

NOTE Confidence: 0.986912882

00:16:17.550 --> 00:16:19.900 animal assays that were specific

NOTE Confidence: 0.986912882

00:16:19.976 --> 00:16:21.778 for psychedelics were discovered,

NOTE Confidence: 0.986912882

00:16:21.778 --> 00:16:23.356 head Twitch response,

NOTE Confidence: 0.986912882

00:16:23.360 --> 00:16:26.258 which I'm going to talk about.

NOTE Confidence: 0.986912882

00:16:26.260 --> 00:16:28.612 A little bit today,

NOTE Confidence: 0.986912882

00:16:28.612 --> 00:16:32.140 the LSD receptor was discovered by.

NOTE Confidence: 0.986912882

00:16:32.140 --> 00:16:34.660 Sol Snyder's group.

NOTE Confidence: 0.986912882

00:16:34.660 --> 00:16:38.706 And then in the 1980s might lab

NOTE Confidence: 0.986912882

00:16:38.706 --> 00:16:42.920 begins studies on signal transduction.

NOTE Confidence: 0.986912882

00:16:42.920 --> 00:16:44.600 5 HT 2A receptors.

NOTE Confidence: 0.986912882

00:16:44.600 --> 00:16:48.652 We found that five HT 2A receptors are

NOTE Confidence: 0.986912882

00:16:48.652 --> 00:16:53.083 localized to pyramidal neurons in the cortex,

NOTE Confidence: 0.986912882

00:16:53.083 --> 00:16:55.167 particularly in apical dendrites.

NOTE Confidence: 0.986912882

00:16:55.170 --> 00:16:57.100 And then, more recently we've

NOTE Confidence: 0.986912882

00:16:57.100 --> 00:16:59.554 been involved in a large number

NOTE Confidence: 0.986912882

00:16:59.554 --> 00:17:01.806 of structural studies of GPCR's,

NOTE Confidence: 0.986912882

00:17:01.806 --> 00:17:04.662 highlighted by the first study showing

NOTE Confidence: 0.986912882

00:17:04.662 --> 00:17:07.989 the structure of LSD bound to a receptor,

NOTE Confidence: 0.986912882

00:17:07.990 --> 00:17:09.554 and then more recently,

NOTE Confidence: 0.986912882

00:17:09.554 --> 00:17:11.900 the structure of a psychedelic bound

NOTE Confidence: 0.986912882

00:17:11.971 --> 00:17:14.190 to a five HT 2A signaling complex.

NOTE Confidence: 0.986912882

00:17:14.190 --> 00:17:16.086 So I'm going to spend a lot of

NOTE Confidence: 0.986912882

00:17:16.086 --> 00:17:17.728 time today talking about this.

NOTE Confidence: 0.986912882

00:17:17.730 --> 00:17:21.266 Uhm, there have been hints in the literature.

NOTE Confidence: 0.986912882

00:17:21.270 --> 00:17:23.510 This really interesting paper by

NOTE Confidence: 0.986912882

00:17:23.510 --> 00:17:26.294 Cameron at all published in Nature

NOTE Confidence: 0.986912882

00:17:26.294 --> 00:17:28.891 earlier this year that we might

NOTE Confidence: 0.986912882

00:17:28.891 --> 00:17:31.697 be able to develop drugs that have

NOTE Confidence: 0.986912882

00:17:31.697 --> 00:17:34.082 some of the potential therapeutic

NOTE Confidence: 0.986912882

00:17:34.082 --> 00:17:36.486 aspects of of psychedelics without

NOTE Confidence: 0.986912882

00:17:36.486 --> 00:17:38.896 the without the psychedelic activity.

NOTE Confidence: 0.986912882

00:17:38.900 --> 00:17:41.220 And I'll talk about that at the end.

NOTE Confidence: 0.986912882

00:17:41.220 --> 00:17:42.780 Uhm?

NOTE Confidence: 0.986912882

00:17:42.780 --> 00:17:44.040 Before I start, though,

NOTE Confidence: 0.986912882

00:17:44.040 --> 00:17:47.272 one of the things I would like to distinguish

NOTE Confidence: 0.986912882

00:17:47.272 --> 00:17:50.560 are psychedelics versus hallucinogens,

NOTE Confidence: 0.986912882

00:17:50.560 --> 00:17:52.960 so there are a number of drugs that

NOTE Confidence: 0.986912882

00:17:52.960 --> 00:17:54.960 induce hallucinations or hallucinogenic

NOTE Confidence: 0.986912882

00:17:54.960 --> 00:17:56.960 life experiences in humans,

NOTE Confidence: 0.986912882

00:17:56.960 --> 00:17:59.520 including salvinorin, A ibogaine,

NOTE Confidence: 0.986912882

00:17:59.520 --> 00:18:02.304 LSD, psilocin, and so on.

NOTE Confidence: 0.986912882

00:18:02.304 --> 00:18:06.150 But psychedelics are defined as LSD like

NOTE Confidence: 0.986912882

00:18:06.150 --> 00:18:09.839 drugs which activate 5 HT 2A receptors,

NOTE Confidence: 0.986912882

00:18:09.840 --> 00:18:12.096 and so those will be the

NOTE Confidence: 0.986912882

00:18:12.096 --> 00:18:13.600 subject of today's talk.

NOTE Confidence: 0.986912882

00:18:13.600 --> 00:18:14.117 Uhm?

NOTE Confidence: 0.986912882

00:18:14.117 --> 00:18:18.253 Now folks like George to a great extent,

NOTE Confidence: 0.986912882

00:18:18.260 --> 00:18:20.934 my lab, perhaps to a lesser extent,

NOTE Confidence: 0.986912882

00:18:20.940 --> 00:18:23.409 have studied psychedelics.

NOTE Confidence: 0.986912882

00:18:23.409 --> 00:18:26.270 Psychedelic drug action really,

NOTE Confidence: 0.986912882

00:18:26.270 --> 00:18:27.050 for many,

NOTE Confidence: 0.986912882

00:18:27.050 --> 00:18:27.830 many decades,

NOTE Confidence: 0.986912882

00:18:27.830 --> 00:18:32.317 sort of up in the backwoods of

NOTE Confidence: 0.986912882

00:18:32.317 --> 00:18:33.992 science because there wasn't

NOTE Confidence: 0.986912882

00:18:33.992 --> 00:18:36.056 wasn't really a lot of interest

NOTE Confidence: 0.986912882

00:18:36.056 --> 00:18:37.933 from the general scientific

NOTE Confidence: 0.986912882

00:18:37.933 --> 00:18:39.897 community about psychedelic drugs,

NOTE Confidence: 0.986912882

00:18:39.900 --> 00:18:42.854 and certainly not a lot of funding,

NOTE Confidence: 0.986912882

00:18:42.860 --> 00:18:45.896 and that that has changed recently.

NOTE Confidence: 0.986912882

00:18:45.900 --> 00:18:48.110 At least interest wise because

NOTE Confidence: 0.986912882

00:18:48.110 --> 00:18:51.403 of some really intriguing phase.

NOTE Confidence: 0.986912882

00:18:51.403 --> 00:18:54.607 Two preliminary clinical studies.

NOTE Confidence: 0.986912882

00:18:54.610 --> 00:18:56.626 And before I summarize these studies,

NOTE Confidence: 0.986912882

00:18:56.630 --> 00:18:59.670 I just I just want to caution everyone

NOTE Confidence: 0.986912882

00:18:59.670 --> 00:19:02.205 that these are not definitive clinical

NOTE Confidence: 0.986912882

00:19:02.205 --> 00:19:05.600 studies and I am not advocating the

NOTE Confidence: 0.986912882

00:19:05.683 --> 00:19:08.405 use of psychedelic drugs for any

NOTE Confidence: 0.986912882

00:19:08.405 --> 00:19:10.880 any sort of psychiatric treatment,

NOTE Confidence: 0.986912882

00:19:10.880 --> 00:19:11.237 but.

NOTE Confidence: 0.986912882

00:19:11.237 --> 00:19:13.379 But the they have attracted a

NOTE Confidence: 0.986912882

00:19:13.379 --> 00:19:14.450 lot of interest,

NOTE Confidence: 0.986912882

00:19:14.450 --> 00:19:16.300 so the first were these

NOTE Confidence: 0.986912882

00:19:16.300 --> 00:19:18.150 studies by Griffiths at all,

NOTE Confidence: 0.986912882

00:19:18.150 --> 00:19:20.978 showing that a single dose so psilocybin,

NOTE Confidence: 0.986912882

00:19:20.980 --> 00:19:23.340 in patients that were depressed

NOTE Confidence: 0.986912882

00:19:23.340 --> 00:19:26.480 induced a rapid in apparently sustained

NOTE Confidence: 0.986912882

00:19:26.480 --> 00:19:27.848 antidepressant anxiolytic response.

NOTE Confidence: 0.986912882

00:19:27.848 --> 00:19:31.040 So you can see here at six

NOTE Confidence: 0.986912882

00:19:31.118 --> 00:19:34.368 months there still was.

NOTE Confidence: 0.986912882

00:19:34.370 --> 00:19:39.280 A clinically significant affect and then,

NOTE Confidence: 0.986912882

00:19:39.280 --> 00:19:40.660 more recently,

NOTE Confidence: 0.986912882

00:19:40.660 --> 00:19:43.272 Carhartt Harrist and colleagues

NOTE Confidence: 0.986912882

00:19:43.272 --> 00:19:45.884 published this interesting again.

NOTE Confidence: 0.986912882

00:19:45.890 --> 00:19:48.088 Phase two trial in the New England

NOTE Confidence: 0.986912882

00:19:48.088 --> 00:19:50.188 Journal of Medicine, showing that, again,

NOTE Confidence: 0.986912882

00:19:50.188 --> 00:19:54.610 in this case, two doses of psilocybin.

NOTE Confidence: 0.986912882

00:19:54.610 --> 00:19:56.910 Induced a.

NOTE Confidence: 0.986912882

00:19:56.910 --> 00:20:00.378 Apparently sustained antidepressant effect.

NOTE Confidence: 0.986912882

00:20:00.378 --> 00:20:04.108 Which was statistically not significantly

NOTE Confidence: 0.986912882

00:20:04.108 --> 00:20:07.780 better than that induced by an SSRI.

NOTE Confidence: 0.986912882

00:20:07.780 --> 00:20:10.750 Although it does look like it

NOTE Confidence: 0.986912882

00:20:10.858 --> 00:20:12.360 it if they increase the end,

NOTE Confidence: 0.986912882

00:20:12.360 --> 00:20:14.235 there might be a statistically

NOTE Confidence: 0.986912882

00:20:14.235 --> 00:20:15.360 significant effect there.

NOTE Confidence: 0.980555004615385

00:20:15.360 --> 00:20:17.502 I just want to note that this is not

NOTE Confidence: 0.980555004615385

00:20:17.502 --> 00:20:20.032 a placebo controlled trial now because

NOTE Confidence: 0.980555004615385

00:20:20.032 --> 00:20:22.524 of results like this and a large

NOTE Confidence: 0.980555004615385

00:20:22.524 --> 00:20:24.799 number of other sort of anecdotal

00:20:24.799 --> 00:20:27.211 or smaller studies, there really

00:20:27.211 --> 00:20:30.553 has been a tremendous interest in.

00:20:30.560 --> 00:20:33.284 In the potential for a psychedelics

00:20:33.284 --> 00:20:35.728 like psilocybin for treating neuro

00:20:35.728 --> 00:20:37.683 psychiatric disorders and and

00:20:37.683 --> 00:20:39.501 hopefully in the next few years

00:20:39.501 --> 00:20:41.544 there will be definitive clinical

00:20:41.544 --> 00:20:45.810 trials shedding light on this. Uhm?

00:20:45.810 --> 00:20:48.946 Now I I basically got into the field

00:20:48.950 --> 00:20:51.998 from a pharmacologic perspective.

00:20:52.000 --> 00:20:55.060 And over the years.

00:20:55.060 --> 00:20:57.200 We've been investigating the pharmacology

00:20:57.200 --> 00:21:00.344 of psychedelics in great detail and to

00:21:00.344 --> 00:21:03.356 summarize a huge number of studies,

00:21:03.360 --> 00:21:05.328 both published and unpublished.

00:21:05.328 --> 00:21:07.788 I can say psychedelics have

NOTE Confidence: 0.980555004615385

00:21:07.788 --> 00:21:10.469 a very complex pharmacology.

NOTE Confidence: 0.980555004615385

00:21:10.470 --> 00:21:12.854 So these are results from a from a

NOTE Confidence: 0.980555004615385

00:21:12.854 --> 00:21:15.188 study we published some years ago

NOTE Confidence: 0.980555004615385

00:21:15.190 --> 00:21:17.890 where we had developed a platform

NOTE Confidence: 0.980555004615385

00:21:17.890 --> 00:21:20.361 whereby we could screen all of the

NOTE Confidence: 0.980555004615385

00:21:20.361 --> 00:21:22.658 G protein coupled receptors in the

NOTE Confidence: 0.980555004615385

00:21:22.658 --> 00:21:25.630 genome in a single 384 well plate.

NOTE Confidence: 0.980555004615385

00:21:25.630 --> 00:21:30.318 And this is a phylogram of of those

NOTE Confidence: 0.980555004615385

00:21:30.318 --> 00:21:33.530 Jeep cars and what I've done here

NOTE Confidence: 0.980555004615385

00:21:33.530 --> 00:21:36.240 is mapped onto that those receptors

NOTE Confidence: 0.980555004615385

00:21:36.240 --> 00:21:39.218 that LSD activates and you can see

NOTE Confidence: 0.980555004615385

00:21:39.218 --> 00:21:40.753 it's basically all the receptors.

NOTE Confidence: 0.980555004615385

00:21:40.760 --> 00:21:43.310 Down here these are all biogenic

NOTE Confidence: 0.980555004615385

00:21:43.310 --> 00:21:45.970 amine receptors. Uhm?

NOTE Confidence: 0.980555004615385

00:21:45.970 --> 00:21:49.135 And interestingly enough.

NOTE Confidence: 0.980555004615385

00:21:49.135 --> 00:21:50.190 Uh.

NOTE Confidence: 0.980555004615385

00:21:50.190 --> 00:21:52.213 Only one of these receptors is actually

NOTE Confidence: 0.980555004615385

00:21:52.213 --> 00:21:54.765 thought to be the the site of action of LSD,

NOTE Confidence: 0.980555004615385

00:21:54.770 --> 00:21:56.720 at least for its psychedelic effects,

NOTE Confidence: 0.980555004615385

00:21:56.720 --> 00:22:00.608 and this is the five HT 2A receptor.

NOTE Confidence: 0.980555004615385

00:22:00.610 --> 00:22:01.717 This is in.

NOTE Confidence: 0.980555004615385

00:22:01.717 --> 00:22:03.562 This isn't quite distinct contrast

NOTE Confidence: 0.980555004615385

00:22:03.562 --> 00:22:05.780 to other hallucinogenic drugs,

NOTE Confidence: 0.980555004615385

00:22:05.780 --> 00:22:07.628 so this is this is another

NOTE Confidence: 0.980555004615385

00:22:07.628 --> 00:22:09.429 hallucinogen we have studied for many,

NOTE Confidence: 0.980555004615385

00:22:09.430 --> 00:22:10.172 many years.

NOTE Confidence: 0.980555004615385

00:22:10.172 --> 00:22:12.395 This is drug salvinorin A which

NOTE Confidence: 0.980555004615385

00:22:12.395 --> 00:22:14.585 is found in this plant salvia,

NOTE Confidence: 0.980555004615385

00:22:14.590 --> 00:22:17.140 which induces a very rapid

NOTE Confidence: 0.980555004615385

00:22:17.140 --> 00:22:19.540 hallucinogenic experience in humans.

NOTE Confidence: 0.980555004615385

00:22:19.540 --> 00:22:23.140 And what we found using basically

00:22:23.227 --> 00:22:25.741 the same platform over the years

00:22:25.741 --> 00:22:28.740 was that it is very selective or the

00:22:28.740 --> 00:22:30.810 Kappa opiate receptor of all the.

00:22:30.810 --> 00:22:32.530 Molecular targets we have screen

00:22:32.530 --> 00:22:34.590 now hundreds and hundreds of them.

00:22:34.590 --> 00:22:36.654 It only interacts with the Kappa

00:22:36.654 --> 00:22:38.477 receptor with high affinity and it

00:22:38.477 --> 00:22:40.282 has relatively weak potency for

00:22:40.282 --> 00:22:43.519 the for the MU receptor and then no

00:22:43.519 --> 00:22:46.503 activity for any other any other target we,

00:22:46.510 --> 00:22:49.667 we or others have ever looked at.

00:22:49.670 --> 00:22:52.060 We've taken advantage of this

00:22:52.060 --> 00:22:54.511 platform that we developed whereby

00:22:54.511 --> 00:22:57.697 we can screen essentially the entire.

00:22:57.700 --> 00:23:01.366 Family of Druggable G protein coupled

NOTE Confidence: 0.980555004615385

00:23:01.366 --> 00:23:01.977 receptors.

NOTE Confidence: 0.980555004615385

00:23:01.980 --> 00:23:04.206 To look at a large number of

NOTE Confidence: 0.980555004615385

00:23:04.206 --> 00:23:04.842 psychoactive drugs,

NOTE Confidence: 0.980555004615385

00:23:04.850 --> 00:23:06.470 including hallucinogens and psychedelics,

NOTE Confidence: 0.980555004615385

00:23:06.470 --> 00:23:08.962 and this is now unpublished data

NOTE Confidence: 0.980555004615385

00:23:08.962 --> 00:23:12.014 and this shows you the data for

NOTE Confidence: 0.980555004615385

00:23:12.014 --> 00:23:15.525 LSD salvinorin A psilocin which is

NOTE Confidence: 0.980555004615385

00:23:15.525 --> 00:23:17.985 the active ingredient psilocybin

NOTE Confidence: 0.980555004615385

00:23:17.990 --> 00:23:19.076 and nor ibogaine,

NOTE Confidence: 0.980555004615385

00:23:19.076 --> 00:23:21.610 which is the active ingredient of Ibogaine,

NOTE Confidence: 0.980555004615385

00:23:21.610 --> 00:23:23.230 and you can see that.

NOTE Confidence: 0.980555004615385

00:23:23.230 --> 00:23:25.150 Nor Ibogaine really only

NOTE Confidence: 0.980555004615385

00:23:25.150 --> 00:23:26.590 activates Kappa receptors.

NOTE Confidence: 0.980555004615385

00:23:26.590 --> 00:23:29.229 There's a little bit of activity at

NOTE Confidence: 0.980555004615385

00:23:29.229 --> 00:23:31.406 this random orphan receptor salvinorin

NOTE Confidence: 0.980555004615385

00:23:31.406 --> 00:23:34.334 has selected for the Kappa receptor.

NOTE Confidence: 0.980555004615385

00:23:34.340 --> 00:23:36.260 And then LSD and psilocin.

NOTE Confidence: 0.980555004615385

00:23:36.260 --> 00:23:37.086 Of course,

NOTE Confidence: 0.980555004615385

00:23:37.086 --> 00:23:39.977 hit many serotonin receptors but also hit.

NOTE Confidence: 0.980555004615385

00:23:39.980 --> 00:23:42.380 Dopamine receptors with fairly

NOTE Confidence: 0.980555004615385

00:23:42.380 --> 00:23:43.580 potent activity.

NOTE Confidence: 0.966170005

00:23:45.780 --> 00:23:48.258 Psilocybin, of course, is a prodrug.

NOTE Confidence: 0.955424976666667

00:23:52.460 --> 00:23:55.670 This phosphate group, here on psilocybin,

NOTE Confidence: 0.955424976666667

00:23:55.670 --> 00:23:57.685 makes it inactive at the

NOTE Confidence: 0.955424976666667

00:23:57.685 --> 00:23:59.608 receptor and following ingestion.

NOTE Confidence: 0.955424976666667

00:23:59.608 --> 00:24:01.632 It's rapidly D phosphorylated

NOTE Confidence: 0.955424976666667

00:24:01.632 --> 00:24:03.972 in the liver to psilocin,

NOTE Confidence: 0.955424976666667

00:24:03.972 --> 00:24:06.027 which is the active ingredient

NOTE Confidence: 0.955424976666667

00:24:06.027 --> 00:24:08.130 in the active metabolite.

NOTE Confidence: 0.955424976666667

00:24:08.130 --> 00:24:11.114 And what we have found is that psilocin

NOTE Confidence: 0.955424976666667

00:24:11.114 --> 00:24:13.746 has high affinity agonist potency

NOTE Confidence: 0.955424976666667

00:24:13.746 --> 00:24:16.686 at nearly all serotonin receptors.

NOTE Confidence: 0.955424976666667

00:24:16.690 --> 00:24:19.096 And this show is sort of

NOTE Confidence: 0.955424976666667

00:24:19.096 --> 00:24:22.380 in in summary format. Uhm?

NOTE Confidence: 0.955424976666667

00:24:22.380 --> 00:24:24.085 All the all the serotonin

NOTE Confidence: 0.955424976666667

00:24:24.085 --> 00:24:26.145 receptors in the genome and you

NOTE Confidence: 0.955424976666667

00:24:26.145 --> 00:24:28.119 can see that for many of these,

NOTE Confidence: 0.955424976666667

00:24:28.120 --> 00:24:30.800 psilocin has very high affinity,

NOTE Confidence: 0.955424976666667

00:24:30.800 --> 00:24:34.867 including all five HT two family receptors,

NOTE Confidence: 0.955424976666667

00:24:34.870 --> 00:24:37.327 and then moderate affinity for others and

NOTE Confidence: 0.955424976666667

00:24:37.327 --> 00:24:40.437 then a weak affinity for the five HT four.

NOTE Confidence: 0.955424976666667

00:24:40.440 --> 00:24:42.204 And it has no affinity for

NOTE Confidence: 0.955424976666667

00:24:42.204 --> 00:24:44.120 the five HT 3 receptor.

NOTE Confidence: 0.955424976666667

00:24:44.120 --> 00:24:47.704 Uhm, we also found that psilocin is

NOTE Confidence: 0.955424976666667

00:24:47.704 --> 00:24:50.949 actually a moderately potent D2 agonist.

NOTE Confidence: 0.955424976666667

00:24:50.950 --> 00:24:52.224 And, uh,

NOTE Confidence: 0.955424976666667

00:24:52.224 --> 00:24:57.320 and this this has not been reported before.

NOTE Confidence: 0.955424976666667

00:24:57.320 --> 00:24:59.336 These data were obtained using a

NOTE Confidence: 0.955424976666667

00:24:59.336 --> 00:25:01.380 new platform that we developed.

NOTE Confidence: 0.955424976666667

00:25:01.380 --> 00:25:05.220 I don't have time to talk to you about today.

NOTE Confidence: 0.955424976666667

00:25:05.220 --> 00:25:06.650 And raises the possibility that

NOTE Confidence: 0.955424976666667

00:25:06.650 --> 00:25:08.819 at least some of the actions that

NOTE Confidence: 0.955424976666667

00:25:08.819 --> 00:25:10.524 site listen might be mediated

NOTE Confidence: 0.955424976666667

00:25:10.524 --> 00:25:12.210 through D2 receptor activation.

NOTE Confidence: 0.955424976666667

00:25:12.210 --> 00:25:13.018 Uhm,

NOTE Confidence: 0.955424976666667

00:25:13.018 --> 00:25:19.497 because it's it's so prominent in in

NOTE Confidence: 0.955424976666667

00:25:19.497 --> 00:25:23.065 research right now we did a a fairly

NOTE Confidence: 0.955424976666667

00:25:23.065 --> 00:25:26.408 deep dive in in the pharmacology of psilocin.

NOTE Confidence: 0.955424976666667

00:25:26.410 --> 00:25:28.965 We found it's a weak partial agonist,

NOTE Confidence: 0.955424976666667

00:25:28.970 --> 00:25:31.270 said five HT 7 receptors.

NOTE Confidence: 0.955424976666667

00:25:31.270 --> 00:25:33.490 This is putative target

NOTE Confidence: 0.955424976666667

00:25:33.490 --> 00:25:35.710 for anti depressant drugs.

NOTE Confidence: 0.955424976666667

00:25:35.710 --> 00:25:36.572 Most worrisome,

NOTE Confidence: 0.955424976666667

00:25:36.572 --> 00:25:41.340 it's a it's an agonist at 5 HT 2B receptors,

NOTE Confidence: 0.955424976666667

00:25:41.340 --> 00:25:45.614 and many years ago we showed that drugs

NOTE Confidence: 0.955424976666667

00:25:45.614 --> 00:25:49.008 that activate 5 HT 2B receptors can

NOTE Confidence: 0.955424976666667

00:25:49.008 --> 00:25:51.096 induce valvular heart disease in humans,

NOTE Confidence: 0.955424976666667

00:25:51.100 --> 00:25:52.374 and a number of them have been

NOTE Confidence: 0.955424976666667

00:25:52.374 --> 00:25:53.220 withdrawn from the market.

NOTE Confidence: 0.955424976666667

00:25:53.220 --> 00:25:56.812 So this is this is potentially a downside

NOTE Confidence: 0.955424976666667

00:25:56.812 --> 00:25:59.959 for repeated psilocybin administration.

NOTE Confidence: 0.955424976666667

00:25:59.960 --> 00:26:01.460 Turns out, most other psychedelics

NOTE Confidence: 0.955424976666667

00:26:01.460 --> 00:26:03.530 interact with five HT 2B receptors,

NOTE Confidence: 0.955424976666667

00:26:03.530 --> 00:26:05.616 so as a class it's a problem.

NOTE Confidence: 0.955424976666667

00:26:05.620 --> 00:26:06.090 For them,

NOTE Confidence: 0.955424976666667

00:26:06.090 --> 00:26:07.735 and it's a weak partial agonist for

NOTE Confidence: 0.955424976666667

00:26:07.735 --> 00:26:09.720 a number of miscellaneous receptors,

NOTE Confidence: 0.955424976666667

00:26:09.720 --> 00:26:12.080 you can see there.

NOTE Confidence: 0.955424976666667

00:26:12.080 --> 00:26:16.232 So, given given this really robust

NOTE Confidence: 0.955424976666667

00:26:16.232 --> 00:26:19.000 pharmacology of these drugs.

NOTE Confidence: 0.955424976666667

00:26:19.000 --> 00:26:21.808 Why is it that we focus on the five

NOTE Confidence: 0.955424976666667

00:26:21.808 --> 00:26:24.811 HT two as the target of psychedelics

NOTE Confidence: 0.955424976666667

00:26:24.811 --> 00:26:27.690 and the initial information came

NOTE Confidence: 0.955424976666667

00:26:27.690 --> 00:26:30.605 from studies in mice by Richard

NOTE Confidence: 0.955424976666667

00:26:30.605 --> 00:26:33.333 Glennon where they were able to

NOTE Confidence: 0.955424976666667

00:26:33.333 --> 00:26:35.810 show that the head Twitch responses

NOTE Confidence: 0.955424976666667

00:26:35.810 --> 00:26:37.770 the psychedelic actions and

NOTE Confidence: 0.955424976666667

00:26:37.770 --> 00:26:39.442 mice correlated very well.

NOTE Confidence: 0.955424976666667

00:26:39.442 --> 00:26:41.806 The potency for a drug inducing

NOTE Confidence: 0.955424976666667

00:26:41.806 --> 00:26:43.880 head Twitch correlated very well

NOTE Confidence: 0.955424976666667

00:26:43.880 --> 00:26:46.280 with five HT 2A receptor affinity.

NOTE Confidence: 0.955424976666667

00:26:46.280 --> 00:26:46.809 Uhm,

NOTE Confidence: 0.955424976666667

00:26:46.809 --> 00:26:49.454 the more definitive studies were

NOTE Confidence: 0.955424976666667

00:26:49.454 --> 00:26:52.230 performed by Gonzalez Maeso in 2007

NOTE Confidence: 0.955424976666667

00:26:52.230 --> 00:26:55.760 and by my lab in 2009 where we showed

NOTE Confidence: 0.955424976666667

00:26:55.760 --> 00:26:58.638 that five HT 2A knockout mice do

NOTE Confidence: 0.955424976666667

00:26:58.638 --> 00:27:00.860 not respond to psychedelic drugs.

NOTE Confidence: 0.955424976666667

00:27:00.860 --> 00:27:04.970 At least the psychedelic like responses.

NOTE Confidence: 0.955424976666667

00:27:04.970 --> 00:27:06.680 But the the most definitive

NOTE Confidence: 0.955424976666667

00:27:06.680 --> 00:27:08.757 studies really are those that have

NOTE Confidence: 0.955424976666667

00:27:08.757 --> 00:27:09.957 been done in humans.

NOTE Confidence: 0.955424976666667

00:27:09.960 --> 00:27:11.532 Franceville Inviters Group was

NOTE Confidence: 0.955424976666667

00:27:11.532 --> 00:27:14.586 the first to show this in 1998.

NOTE Confidence: 0.955424976666667

00:27:14.586 --> 00:27:16.758 He showed that cancer,

NOTE Confidence: 0.955424976666667

00:27:16.760 --> 00:27:18.866 in which is a five HT,

NOTE Confidence: 0.955424976666667

00:27:18.870 --> 00:27:20.484 2A preferring antagonist,

NOTE Confidence: 0.955424976666667

00:27:20.484 --> 00:27:23.174 blocked essentially all the actions

NOTE Confidence: 0.955424976666667

00:27:23.174 --> 00:27:26.115 of psilocybin in human volunteers and

NOTE Confidence: 0.955424976666667

00:27:26.115 --> 00:27:28.240 then more recently several groups

NOTE Confidence: 0.955424976666667

00:27:28.240 --> 00:27:30.941 have shown that virtually all of the

NOTE Confidence: 0.955424976666667

00:27:30.941 --> 00:27:33.111 effects of LSD are fully blocked by

NOTE Confidence: 0.966717679333334

00:27:33.184 --> 00:27:35.880 cancer and so it does appear that it's

NOTE Confidence: 0.966717679333334

00:27:35.880 --> 00:27:40.030 most likely that five HT 2A receptor.

NOTE Confidence: 0.966717679333334

00:27:40.030 --> 00:27:44.236 Now, if you were to zoom out.

NOTE Confidence: 0.966717679333334

00:27:44.236 --> 00:27:48.514 And look at all known psychedelics.

NOTE Confidence: 0.966717679333334

00:27:48.520 --> 00:27:51.388 As well as drugs which have.

NOTE Confidence: 0.966717679333334

00:27:51.390 --> 00:27:54.300 Structure similar to psychedelics but are

NOTE Confidence: 0.966717679333334

00:27:54.300 --> 00:27:57.084 not psychedelic in humans like listia

NOTE Confidence: 0.966717679333334

00:27:57.084 --> 00:28:01.698 ride and bromo LSD and screen them against

NOTE Confidence: 0.966717679333334

00:28:01.698 --> 00:28:04.758 a number of important neurotransmitter

NOTE Confidence: 0.966717679333334

00:28:04.758 --> 00:28:07.878 receptors which we have done.

NOTE Confidence: 0.966717679333334

00:28:07.880 --> 00:28:11.399 Uhm, you would get a heat map like this.

NOTE Confidence: 0.966717679333334

00:28:11.400 --> 00:28:13.910 And, uh, given these results,

NOTE Confidence: 0.966717679333334

00:28:13.910 --> 00:28:17.478 it would be very difficult or impossible to.

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NOTE Confidence: 0.966717679333334

00:28:17.480 --> 00:28:20.315 To show that this one receptor here

NOTE Confidence: 0.966717679333334

00:28:20.315 --> 00:28:23.799 5 HT 2A receptor is responsible

NOTE Confidence: 0.966717679333334

00:28:23.800 --> 00:28:25.548 for the psychedelic activity.

NOTE Confidence: 0.966717679333334

00:28:25.548 --> 00:28:26.859 But it does,

NOTE Confidence: 0.966717679333334

00:28:26.860 --> 00:28:29.704 it does appear that that is indeed the case.

NOTE Confidence: 0.966717679333334

00:28:29.710 --> 00:28:30.300 Uhm?

NOTE Confidence: 0.974582933333333

00:28:33.540 --> 00:28:36.102 The consequences of this are that these

NOTE Confidence: 0.974582933333333

00:28:36.102 --> 00:28:38.656 drugs are potent 5 HT, 2B agonists.

NOTE Confidence: 0.974582933333333

00:28:38.656 --> 00:28:41.824 These can cause gobler heart disease.

NOTE Confidence: 0.974582933333333

00:28:41.830 --> 00:28:44.285 Many drugs with structural and

NOTE Confidence: 0.974582933333333

00:28:44.285 --> 00:28:46.249 pharmacologic similarity to LSD

NOTE Confidence: 0.974582933333333

00:28:46.249 --> 00:28:49.087 have been withdrawn from the market.

NOTE Confidence: 0.974582933333333

00:28:49.090 --> 00:28:50.236 Interestingly enough,

NOTE Confidence: 0.974582933333333

00:28:50.236 --> 00:28:53.674 ecstasy also activates 5 HT 2B.

NOTE Confidence: 0.974582933333333

00:28:53.680 --> 00:28:55.904 This is something we showed many years ago.

NOTE Confidence: 0.974582933333333

00:28:55.910 --> 00:28:58.136 Chronic ecstasy use can also be

NOTE Confidence: 0.974582933333333

00:28:58.136 --> 00:29:00.160 associated with valvular heart disease.

NOTE Confidence: 0.974582933333333

00:29:00.160 --> 00:29:02.344 And the big unknown here is it's

NOTE Confidence: 0.974582933333333

00:29:02.344 --> 00:29:04.610 unknown which of the many additional

NOTE Confidence: 0.974582933333333

00:29:04.610 --> 00:29:06.720 receptors targeted by these drugs

NOTE Confidence: 0.974582933333333

00:29:06.720 --> 00:29:09.655 are associated with either side

NOTE Confidence: 0.974582933333333

00:29:09.655 --> 00:29:12.003 effects or therapeutic actions.

NOTE Confidence: 0.974582933333333

00:29:12.010 --> 00:29:15.436 Uhm, now our current understanding of

NOTE Confidence: 0.974582933333333

00:29:15.436 --> 00:29:18.699 psilocybin actions are shown here and

NOTE Confidence: 0.974582933333333

00:29:18.699 --> 00:29:21.793 I'm going to go through this diagram.

NOTE Confidence: 0.974582933333333

00:29:21.800 --> 00:29:23.982 In a little bit of detail highlighting

NOTE Confidence: 0.974582933333333

00:29:23.982 --> 00:29:26.514 results from our labs and others,

NOTE Confidence: 0.974582933333333

00:29:26.520 --> 00:29:29.173 and this is from a review which

NOTE Confidence: 0.974582933333333

00:29:29.173 --> 00:29:31.549 hopefully will be published soon.

NOTE Confidence: 0.974582933333333

00:29:31.550 --> 00:29:35.944 So five HT 2A receptors are found primarily,

NOTE Confidence: 0.974582933333333

00:29:35.944 --> 00:29:38.320 although not exclusively,

NOTE Confidence: 0.974582933333333

00:29:38.320 --> 00:29:41.236 in layer five cortical pyramidal neurons.

NOTE Confidence: 0.974582933333333

00:29:41.240 --> 00:29:42.928 This is a discovery.

NOTE Confidence: 0.974582933333333

00:29:42.928 --> 00:29:45.460 My lab made many years ago,

NOTE Confidence: 0.974582933333333

00:29:45.460 --> 00:29:47.740 now subsequently course verified

NOTE Confidence: 0.974582933333333

00:29:47.740 --> 00:29:49.450 by many others.

NOTE Confidence: 0.895594548

00:29:51.870 --> 00:29:56.182 And a five HT 2A receptors induce a

NOTE Confidence: 0.895594548

00:29:56.182 --> 00:29:58.892 very complicated series of downstream

NOTE Confidence: 0.895594548

00:29:58.892 --> 00:30:00.630 signaling cascades, which which

NOTE Confidence: 0.895594548

00:30:00.630 --> 00:30:02.905 I'll talk a little bit about today.

NOTE Confidence: 0.895594548

00:30:02.910 --> 00:30:07.210 I first got my start studying these in 1984

NOTE Confidence: 0.895594548

00:30:07.210 --> 00:30:10.944 when I was in MIMO, Costas Lab and we.

NOTE Confidence: 0.895594548

00:30:10.944 --> 00:30:13.299 We basically discovered this pathway

NOTE Confidence: 0.895594548

00:30:13.299 --> 00:30:16.775 for five HT 2A receptors. Uhm, and then,

NOTE Confidence: 0.895594548

00:30:16.775 --> 00:30:21.130 uh, you know many years later, uh?

NOTE Confidence: 0.895594548

00:30:21.130 --> 00:30:23.804 We, along with Peter Penzeys were were

NOTE Confidence: 0.895594548

00:30:23.804 --> 00:30:26.806 the first to show that psychedelic drugs

NOTE Confidence: 0.895594548

00:30:26.806 --> 00:30:29.939 can induce a spine formation in neurons

NOTE Confidence: 0.895594548

00:30:29.939 --> 00:30:32.440 and Alex Kwan's lab recently published

NOTE Confidence: 0.895594548

00:30:32.440 --> 00:30:34.990 a beautiful paper and neuron showing

NOTE Confidence: 0.895594548

00:30:35.058 --> 00:30:37.704 that a single dose of psilocybin induces

NOTE Confidence: 0.895594548

00:30:37.704 --> 00:30:41.208 a sustained increase in spine formation.

NOTE Confidence: 0.895594548

00:30:41.210 --> 00:30:44.534 Uhm? So, as I mentioned,

NOTE Confidence: 0.895594548

00:30:44.534 --> 00:30:47.242 five HT 2A receptors are localized to

NOTE Confidence: 0.895594548

00:30:47.242 --> 00:30:49.360 these April dendrites of pyramidal

NOTE Confidence: 0.895594548

00:30:49.360 --> 00:30:51.560 neurons in the cerebral cortex.

NOTE Confidence: 0.895594548

00:30:51.560 --> 00:30:54.857 Uhm, and they coupled to a large

NOTE Confidence: 0.895594548

00:30:54.857 --> 00:30:57.879 number of downstream signaling events.

NOTE Confidence: 0.895594548

00:30:57.880 --> 00:31:00.016 Five HT 2A receptors are primarily

NOTE Confidence: 0.895594548

00:31:00.016 --> 00:31:02.275 coupled to a geographique you where

NOTE Confidence: 0.895594548

00:31:02.275 --> 00:31:03.819 they promote calcium release.

NOTE Confidence: 0.895594548

00:31:03.820 --> 00:31:06.160 This can also lead to activation

NOTE Confidence: 0.895594548

00:31:06.160 --> 00:31:08.856 of protein kinase C as well.

NOTE Confidence: 0.895594548

00:31:08.856 --> 00:31:12.000 The receptors engage arrest in which

NOTE Confidence: 0.895594548

00:31:12.000 --> 00:31:14.100 likely is responsible for at least some

NOTE Confidence: 0.895594548

00:31:14.100 --> 00:31:16.440 of the actions of psychedelic drugs,

NOTE Confidence: 0.895594548

00:31:16.440 --> 00:31:19.008 which I'll I'll show you shortly.

NOTE Confidence: 0.895594548

00:31:19.010 --> 00:31:21.755 Uhm, and these are basically

NOTE Confidence: 0.895594548

00:31:21.755 --> 00:31:24.500 all findings from my lab.

NOTE Confidence: 0.895594548

00:31:24.500 --> 00:31:27.932 Uhm? Most importantly,

NOTE Confidence: 0.895594548

00:31:27.932 --> 00:31:31.688 after all of these things happen.

NOTE Confidence: 0.895594548

00:31:31.690 --> 00:31:33.650 There's increased excitability of

NOTE Confidence: 0.895594548

00:31:33.650 --> 00:31:36.295 these neurons, and as mentioned,

NOTE Confidence: 0.895594548

00:31:36.295 --> 00:31:39.625 this was discovered by George Janion.

NOTE Confidence: 0.895594548

00:31:39.630 --> 00:31:44.130 Uh, and really a Seminole paper.

NOTE Confidence: 0.895594548

00:31:44.130 --> 00:31:46.914 Was by Gerard Merrick and and George where

NOTE Confidence: 0.895594548

00:31:46.914 --> 00:31:49.418 they showed that there was an increase.

NOTE Confidence: 0.895594548

00:31:49.420 --> 00:31:50.640 In a.

NOTE Confidence: 0.978187573

00:31:52.760 --> 00:31:56.702 It excitability in layer 5 pyramidal

NOTE Confidence: 0.978187573

00:31:56.702 --> 00:31:59.330 neurons induced by psychedelics.

NOTE Confidence: 0.978187573

00:31:59.330 --> 00:32:03.474 Uhm? Now we and and this is likely

NOTE Confidence: 0.978187573

00:32:03.474 --> 00:32:07.397 mediated through this sort of very

NOTE Confidence: 0.978187573

00:32:07.397 --> 00:32:09.485 complicated signaling cascade.

NOTE Confidence: 0.978187573

00:32:09.490 --> 00:32:11.278 This is from a review article

NOTE Confidence: 0.978187573

00:32:11.278 --> 00:32:14.309 that we published in 1987 and you

NOTE Confidence: 0.978187573

00:32:14.309 --> 00:32:18.600 can see it differs only from the

NOTE Confidence: 0.978187573

00:32:18.600 --> 00:32:21.006 2021 version by being in black

NOTE Confidence: 0.978187573

00:32:21.006 --> 00:32:23.160 and white rather than color.

NOTE Confidence: 0.98986343

00:32:26.430 --> 00:32:30.140 So, So what? What George and others

NOTE Confidence: 0.98986343

00:32:30.140 --> 00:32:34.056 have shown is that when and we've been

NOTE Confidence: 0.98986343

00:32:34.056 --> 00:32:37.572 able to verify these results in our lab

NOTE Confidence: 0.98986343

00:32:37.572 --> 00:32:40.715 using reporter mice in which we are able

NOTE Confidence: 0.98986343

00:32:40.715 --> 00:32:43.402 to do electrophysiological recordings

NOTE Confidence: 0.98986343

00:32:43.402 --> 00:32:47.986 on five HT 2A identified neurons.

NOTE Confidence: 0.98986343

00:32:47.990 --> 00:32:51.065 Is that acute administration of

NOTE Confidence: 0.98986343

00:32:51.065 --> 00:32:53.864 psychedelics to Abbath increase caused

NOTE Confidence: 0.98986343

00:32:53.864 --> 00:32:56.249 this immediate increase in excitability?

NOTE Confidence: 0.983294471111111

00:32:58.450 --> 00:32:59.656 But there's there's a little bit

NOTE Confidence: 0.983294471111111

00:32:59.656 --> 00:33:01.988 more to that, and this is this is a

NOTE Confidence: 0.983294471111111

00:33:01.988 --> 00:33:04.688 study that I did with a very talented

NOTE Confidence: 0.983294471111111

00:33:04.688 --> 00:33:07.917 technician in my lab, Sandy, who fison.

NOTE Confidence: 0.983294471111111

00:33:07.917 --> 00:33:12.560 Uh, well we have cortical neurons in there.

NOTE Confidence: 0.983294471111111

00:33:12.560 --> 00:33:15.450 Expressing a calcium reporter and

NOTE Confidence: 0.983294471111111

00:33:15.450 --> 00:33:18.630 we're going to Bath applied I.

NOTE Confidence: 0.983294471111111

00:33:18.630 --> 00:33:21.114 Uh, and you can see immediately

NOTE Confidence: 0.983294471111111

00:33:21.114 --> 00:33:23.829 there is this burst of activity,

NOTE Confidence: 0.983294471111111

00:33:23.830 --> 00:33:26.158 but if you look closely here.

NOTE Confidence: 0.983294471111111

00:33:26.160 --> 00:33:27.564 At the neurons.

NOTE Confidence: 0.983294471111111

00:33:27.564 --> 00:33:29.700 You'll see, in addition to the burst,

NOTE Confidence: 0.983294471111111

00:33:29.700 --> 00:33:33.438 there's also this sort of spontaneous

NOTE Confidence: 0.983294471111111

00:33:33.438 --> 00:33:35.930 increase in spontaneous activity.

NOTE Confidence: 0.983294471111111

00:33:35.930 --> 00:33:38.590 And when a large number

NOTE Confidence: 0.983294471111111

00:33:38.590 --> 00:33:40.718 of neurons are quantified.

NOTE Confidence: 0.983294471111111

00:33:40.720 --> 00:33:42.120 You see something like this,

NOTE Confidence: 0.983294471111111

00:33:42.120 --> 00:33:44.469 so this is a pre drug and you can

NOTE Confidence: 0.983294471111111

00:33:44.469 --> 00:33:47.057 see that most neurons are quiescent,

NOTE Confidence: 0.983294471111111

00:33:47.060 --> 00:33:49.636 although there are some that are active.

NOTE Confidence: 0.983294471111111

00:33:49.640 --> 00:33:50.690 When the drug is applied,

NOTE Confidence: 0.983294471111111

00:33:50.690 --> 00:33:51.878 there's this gradient,

NOTE Confidence: 0.983294471111111

00:33:51.878 --> 00:33:52.670 increasing excitability,

NOTE Confidence: 0.983294471111111

00:33:52.670 --> 00:33:56.936 and then there is this sustained.

NOTE Confidence: 0.983294471111111

00:33:56.940 --> 00:33:59.808 Increase in what looks like noise.

NOTE Confidence: 0.983294471111111

00:33:59.810 --> 00:34:02.726 And what we suspect is that

NOTE Confidence: 0.983294471111111

00:34:02.726 --> 00:34:05.260 it's it's actually not this.

NOTE Confidence: 0.983294471111111

00:34:05.260 --> 00:34:05.806 Response,

NOTE Confidence: 0.983294471111111

00:34:05.806 --> 00:34:09.082 but it's this response this this

NOTE Confidence: 0.983294471111111

00:34:09.082 --> 00:34:11.598 noise that's injected into the

NOTE Confidence: 0.983294471111111

00:34:11.598 --> 00:34:13.902 system that is responsible for

NOTE Confidence: 0.983294471111111

00:34:13.902 --> 00:34:15.732 the psychedelic drug actions

NOTE Confidence: 0.983294471111111

00:34:15.732 --> 00:34:18.037 on layer 5 pyramidal neurons.

NOTE Confidence: 0.990097287

00:34:20.140 --> 00:34:22.126 Now how this occurs is is

NOTE Confidence: 0.990097287

00:34:22.126 --> 00:34:23.450 still not entirely clear.

NOTE Confidence: 0.990097287

00:34:23.450 --> 00:34:27.458 We we we have pretty good pretty good

NOTE Confidence: 0.990097287

00:34:27.458 --> 00:34:30.200 data suggesting that GQ might be involved,

NOTE Confidence: 0.990097287

00:34:30.200 --> 00:34:32.387 and as I'll show you a little bit later,

NOTE Confidence: 0.990097287

00:34:32.390 --> 00:34:35.828 arrested might be involved and there

NOTE Confidence: 0.990097287

00:34:35.828 --> 00:34:39.934 also is now some evidence that various

NOTE Confidence: 0.990097287

00:34:39.934 --> 00:34:43.290 kinases downstream might be involved.

NOTE Confidence: 0.990097287

00:34:43.290 --> 00:34:47.403 Uhm, this is this is interesting to us

NOTE Confidence: 0.990097287

00:34:47.403 --> 00:34:51.260 because we had some years ago found that.

00:34:54.040 --> 00:34:56.119 There's interesting kinase

00:34:56.119 --> 00:34:58.198 ribosomal S6 kinase.

00:34:58.200 --> 00:35:00.575 Can directly interact with five

00:35:00.575 --> 00:35:04.190 HT 2A receptors. Yeah, in vivo.

00:35:04.190 --> 00:35:08.895 And that it phosphorylates 5 HT 2A

00:35:08.895 --> 00:35:12.465 receptors and then more recently in

00:35:12.465 --> 00:35:14.950 collaboration with the Krogan and who

00:35:14.950 --> 00:35:17.670 to 9 lab a really talented postdoc.

00:35:17.670 --> 00:35:21.995 Xiaofeng Zhang has done unbiased

00:35:21.995 --> 00:35:24.874 phosphoproteomic studies of cells

00:35:24.874 --> 00:35:27.734 expressing 5 HT 2A receptors

00:35:27.740 --> 00:35:30.020 where they've been exposed to

00:35:30.020 --> 00:35:32.550 the non hallucinogenic 5 HT 2A

00:35:32.550 --> 00:35:35.360 agonist lysher rider cellulose in.

00:35:35.360 --> 00:35:37.802 And you can see that psilocin

NOTE Confidence: 0.976907176666667

00:35:37.802 --> 00:35:39.430 causes increase in phosphorylation

NOTE Confidence: 0.976907176666667

00:35:39.495 --> 00:35:41.337 of a huge number of proteins.

NOTE Confidence: 0.976907176666667

00:35:41.340 --> 00:35:43.995 I just want to mention here that GSK 3

NOTE Confidence: 0.976907176666667

00:35:43.995 --> 00:35:47.047 beta phosphorylation actually is diminished.

NOTE Confidence: 0.976907176666667

00:35:47.050 --> 00:35:48.750 Uh, but in particular, many,

NOTE Confidence: 0.976907176666667

00:35:48.750 --> 00:35:50.750 many ribosomal S6 kinase is,

NOTE Confidence: 0.976907176666667

00:35:50.750 --> 00:35:52.830 and so we think.

NOTE Confidence: 0.976907176666667

00:35:52.830 --> 00:35:54.450 We think that this actually

NOTE Confidence: 0.976907176666667

00:35:54.450 --> 00:35:57.128 may be one of the keys to the

NOTE Confidence: 0.976907176666667

00:35:57.128 --> 00:35:58.480 effects of psychedelic drugs,

NOTE Confidence: 0.976907176666667

00:35:58.480 --> 00:36:00.552 and we're investigating that

NOTE Confidence: 0.976907176666667

00:36:00.552 --> 00:36:04.260 in great detail the other.

NOTE Confidence: 0.976907176666667

00:36:04.260 --> 00:36:06.600 Other sort of studies that we're

NOTE Confidence: 0.976907176666667

00:36:06.600 --> 00:36:09.703 doing now to give you a peek at

NOTE Confidence: 0.976907176666667

00:36:09.703 --> 00:36:11.523 at at some unpublished data.

NOTE Confidence: 0.976907176666667

00:36:11.530 --> 00:36:14.442 Has has been to begin to understand

NOTE Confidence: 0.976907176666667

00:36:14.442 --> 00:36:18.136 what the more long term consequences of

NOTE Confidence: 0.976907176666667

00:36:18.136 --> 00:36:20.080 psychedelic Drug Administration might

NOTE Confidence: 0.976907176666667

00:36:20.080 --> 00:36:23.480 be having on on the transcription,

NOTE Confidence: 0.976907176666667

00:36:23.480 --> 00:36:24.004 transcriptome,

NOTE Confidence: 0.976907176666667

00:36:24.004 --> 00:36:25.576 and transcriptional machinery.

NOTE Confidence: 0.976907176666667

00:36:25.576 --> 00:36:28.359 And for this, we've taken advantage

NOTE Confidence: 0.976907176666667

00:36:28.359 --> 00:36:30.777 of a mouse we have created.

NOTE Confidence: 0.976907176666667

00:36:30.780 --> 00:36:33.912 Uh, which has a tagged 5 HT 2A receptor.

NOTE Confidence: 0.976907176666667

00:36:33.920 --> 00:36:35.906 I'll be showing you this in

NOTE Confidence: 0.976907176666667

00:36:35.906 --> 00:36:38.004 a minute and pre recombinase.

NOTE Confidence: 0.976907176666667

00:36:38.004 --> 00:36:40.872 This was made by crisper technology.

NOTE Confidence: 0.976907176666667

00:36:40.880 --> 00:36:43.344 We cross this with a raibow tag

NOTE Confidence: 0.976907176666667

00:36:43.344 --> 00:36:46.340 mouse so that the rybo tag.

NOTE Confidence: 0.976907176666667

00:36:46.340 --> 00:36:50.078 This isn't a tagged ribosomal subunit.

NOTE Confidence: 0.976907176666667

00:36:50.080 --> 00:36:53.110 Is expressed only in five HT.

NOTE Confidence: 0.976907176666667

00:36:53.110 --> 00:36:54.132 2A neurons.

NOTE Confidence: 0.976907176666667

00:36:54.132 --> 00:36:58.220 This allows us then to do Ribault seek.

NOTE Confidence: 0.976907176666667

00:36:58.220 --> 00:37:01.560 Ribault Tag high throughput sequencing.

NOTE Confidence: 0.976907176666667

00:37:01.560 --> 00:37:03.920 So basically what we can do is we

NOTE Confidence: 0.976907176666667

00:37:03.920 --> 00:37:05.899 can isolate nascent transcripts.

NOTE Confidence: 0.976907176666667

00:37:05.900 --> 00:37:09.164 From neurons that only are expressing

NOTE Confidence: 0.976907176666667

00:37:09.164 --> 00:37:13.101 5 HT 2A receptors before and after

NOTE Confidence: 0.976907176666667

00:37:13.101 --> 00:37:14.862 administration of psychedelic

NOTE Confidence: 0.976907176666667

00:37:14.862 --> 00:37:17.210 and non psychedelic drugs.

NOTE Confidence: 0.976907176666667

00:37:17.210 --> 00:37:18.706 And this is the.

NOTE Confidence: 0.976907176666667

00:37:18.706 --> 00:37:21.372 This is a volcano plot shows you

NOTE Confidence: 0.976907176666667

00:37:21.372 --> 00:37:23.370 the sort of data we get.

NOTE Confidence: 0.976907176666667

00:37:23.370 --> 00:37:25.904 This is a studies done by really

NOTE Confidence: 0.976907176666667

00:37:25.904 --> 00:37:28.118 talented student of mine, Jeff Berto.

NOTE Confidence: 0.976907176666667

00:37:28.118 --> 00:37:30.950 What we found is actually more than 1000.

NOTE Confidence: 0.976907176666667

00:37:30.950 --> 00:37:33.551 Transcripts are relatively

00:37:33.551 --> 00:37:37.956 rapidly regulated by this five HT,

00:37:37.956 --> 00:37:39.828 2A preferring psychedelic drug,

00:37:39.830 --> 00:37:41.339 25 cyano envo.

00:37:41.339 --> 00:37:42.848 And by contrast,

00:37:42.850 --> 00:37:45.034 the drug glycerides which is non psychedelic.

00:37:47.060 --> 00:37:48.730 Caused only about a dozen

00:37:48.730 --> 00:37:50.066 transcripts to be changed,

00:37:50.070 --> 00:37:52.790 so we think this this may be a

00:37:52.790 --> 00:37:55.410 signature for psychedelic drug action.

00:37:55.410 --> 00:37:57.447 When we did a dive into the,

00:37:57.450 --> 00:38:02.208 uh, uh, what types of UM?

00:38:02.210 --> 00:38:03.800 Transcripts were altered.

00:38:03.800 --> 00:38:07.510 You can see that it's many of

00:38:07.608 --> 00:38:10.500 them involved in neurogenesis.

00:38:10.500 --> 00:38:15.084 Spine formation and so on are are among

NOTE Confidence: 0.984863317777778

00:38:15.084 --> 00:38:22.228 the leading candidates and and so this is.

NOTE Confidence: 0.984863317777778

00:38:22.228 --> 00:38:24.216 This is pretty interesting,

NOTE Confidence: 0.984863317777778

00:38:24.220 --> 00:38:27.560 and as we go further I think will give us.

NOTE Confidence: 0.984863317777778

00:38:27.560 --> 00:38:29.936 More clues into what?

NOTE Confidence: 0.984863317777778

00:38:29.936 --> 00:38:33.865 What might the basis for some of these

NOTE Confidence: 0.984863317777778

00:38:33.865 --> 00:38:36.010 long lasting effects of psychedelic

NOTE Confidence: 0.984863317777778

00:38:36.091 --> 00:38:38.021 drugs be beyond just changing

NOTE Confidence: 0.984863317777778

00:38:38.021 --> 00:38:40.680 the number of spines on a neuron.

NOTE Confidence: 0.984863317777778

00:38:40.680 --> 00:38:43.438 Uhm, I want to spend the rest

NOTE Confidence: 0.984863317777778

00:38:43.438 --> 00:38:45.400 of the time though.

NOTE Confidence: 0.984863317777778

00:38:45.400 --> 00:38:48.208 Focusing on really what has been

NOTE Confidence: 0.984863317777778

00:38:48.208 --> 00:38:51.368 a long journey for me in my lab.

NOTE Confidence: 0.984863317777778

00:38:51.370 --> 00:38:54.810 Which is to understand how drugs like LSD.

NOTE Confidence: 0.984863317777778

00:38:54.810 --> 00:38:57.618 Bind to and activate these receptors,

NOTE Confidence: 0.984863317777778

00:38:57.620 --> 00:39:00.245 since it appears that these are the

NOTE Confidence: 0.984863317777778

00:39:00.245 --> 00:39:02.300 receptors responsible for their actions.

NOTE Confidence: 0.984863317777778

00:39:02.300 --> 00:39:04.708 And to give you a sense of

NOTE Confidence: 0.984863317777778

00:39:04.708 --> 00:39:06.780 how long this journey is,

NOTE Confidence: 0.984863317777778

00:39:06.780 --> 00:39:09.548 this is one of my first papers published.

NOTE Confidence: 0.975059362222222

00:39:11.700 --> 00:39:13.644 Add and summarized his work that

NOTE Confidence: 0.975059362222222

00:39:13.644 --> 00:39:16.249 was begun when I first started my

NOTE Confidence: 0.975059362222222

00:39:16.249 --> 00:39:18.314 faculty position at case Western.

NOTE Confidence: 0.975059362222222

00:39:18.320 --> 00:39:23.682 Uh, in 1991. This is the first.

NOTE Confidence: 0.975059362222222

00:39:23.682 --> 00:39:27.060 Color cover of the journal

NOTE Confidence: 0.975059362222222

00:39:27.060 --> 00:39:28.430 Molecular Pharmacology.

NOTE Confidence: 0.975059362222222

00:39:28.430 --> 00:39:32.172 And what we did was we did

NOTE Confidence: 0.975059362222222

00:39:32.172 --> 00:39:34.260 molecular modeling and site

NOTE Confidence: 0.975059362222222

00:39:34.260 --> 00:39:35.826 directed mutagenesis studies.

NOTE Confidence: 0.975059362222222

00:39:35.830 --> 00:39:37.930 Of course we didn't have any receptor

NOTE Confidence: 0.975059362222222

00:39:37.930 --> 00:39:39.796 structures in those days to try

NOTE Confidence: 0.975059362222222

00:39:39.796 --> 00:39:41.884 to understand how drugs like LSD.

NOTE Confidence: 0.975059362222222

00:39:41.890 --> 00:39:45.236 You can see here as well as

NOTE Confidence: 0.975059362222222

00:39:45.236 --> 00:39:47.270 this non psychedelic drug.

NOTE Confidence: 0.975059362222222

00:39:47.270 --> 00:39:49.552 I hide your origami how they might

NOTE Confidence: 0.975059362222222

00:39:49.552 --> 00:39:51.478 interact with five HT 2A receptors

NOTE Confidence: 0.975059362222222

00:39:51.478 --> 00:39:54.550 and what what we proposed actually was

NOTE Confidence: 0.975059362222222

00:39:54.550 --> 00:39:58.638 that there were key residues here for.

NOTE Confidence: 0.975059362222222

00:39:58.640 --> 00:40:01.155 For specifying LSD action and

NOTE Confidence: 0.975059362222222

00:40:01.155 --> 00:40:02.968 that the non psychedelic drugs

NOTE Confidence: 0.975059362222222

00:40:02.968 --> 00:40:04.603 actually would bind differently to

NOTE Confidence: 0.975059362222222

00:40:04.603 --> 00:40:06.358 the receptor then psychedelics.

NOTE Confidence: 0.98894496

00:40:09.450 --> 00:40:13.590 If we go forward. Uhm?

NOTE Confidence: 0.98894496

00:40:13.590 --> 00:40:17.546 In a in a series of papers first published

NOTE Confidence: 0.98894496

00:40:17.546 --> 00:40:20.714 by Daniel Wacker from my lab in 2017

NOTE Confidence: 0.98894496

00:40:20.714 --> 00:40:24.879 and then more recently by Koo Kim,

NOTE Confidence: 0.98894496

00:40:24.880 --> 00:40:27.940 we were able to understand the

NOTE Confidence: 0.98894496

00:40:27.940 --> 00:40:30.680 actions of psychedelic drugs at the.

NOTE Confidence: 0.98894496

00:40:30.680 --> 00:40:34.250 Near atomic level by X ray crystallography

NOTE Confidence: 0.98894496

00:40:34.250 --> 00:40:36.810 and cryo electron microscopy.

NOTE Confidence: 0.98894496

00:40:36.810 --> 00:40:38.666 And before I show you the data I

NOTE Confidence: 0.98894496

00:40:38.666 --> 00:40:40.690 want to show you this little movie

NOTE Confidence: 0.98894496

00:40:40.690 --> 00:40:43.225 here which was produced by Gabriel

NOTE Confidence: 0.98894496

00:40:43.225 --> 00:40:45.913 Ashlynn of Ribose Film Studios and

NOTE Confidence: 0.98894496

00:40:45.913 --> 00:40:48.524 this was presented on the very last

NOTE Confidence: 0.98894496

00:40:48.524 --> 00:40:50.776 episode of Hamilton's Pharmacopia.

NOTE Confidence: 0.98894496

00:40:50.776 --> 00:40:55.790 And this is LSD and.

NOTE Confidence: 0.98894496

00:40:55.790 --> 00:40:58.748 Uh, for those of you who?

NOTE Confidence: 0.98894496

00:40:58.750 --> 00:41:02.089 Uh, we'll find the rest of what I present.

NOTE Confidence: 0.98894496

00:41:02.090 --> 00:41:08.036 Somewhat mystifying or too much for the

NOTE Confidence: 0.98894496

00:41:08.036 --> 00:41:10.004 specialists II urge you just to watch this,

NOTE Confidence: 0.98894496

00:41:10.010 --> 00:41:11.972 because all of the key points are are in

NOTE Confidence: 0.98894496

00:41:11.972 --> 00:41:15.360 this little movie here, so here's lsted.

NOTE Confidence: 0.98894496

00:41:15.360 --> 00:41:19.136 Uhm? It's flying through space.

NOTE Confidence: 0.98894496

00:41:19.136 --> 00:41:21.180 Imagine someone has just taken LSD.

NOTE Confidence: 0.98894496

00:41:21.180 --> 00:41:24.850 It's. Flying through their body.

NOTE Confidence: 0.98894496

00:41:24.850 --> 00:41:28.562 And soon it's going to come in close

NOTE Confidence: 0.98894496

00:41:28.562 --> 00:41:31.098 communication with the receptor here.

NOTE Confidence: 0.98894496

00:41:31.100 --> 00:41:33.158 And here you can see the five

NOTE Confidence: 0.98894496

00:41:33.158 --> 00:41:35.109 HT 2A receptor there in white.

NOTE Confidence: 0.98894496

00:41:35.110 --> 00:41:37.468 You can see the large extracellular

NOTE Confidence: 0.98894496

00:41:37.468 --> 00:41:38.647 amino terminus there,

NOTE Confidence: 0.98894496

00:41:38.650 --> 00:41:41.499 floating and LSD sort of bounces around

NOTE Confidence: 0.98894496

00:41:41.499 --> 00:41:45.150 for a little while before it finds this

NOTE Confidence: 0.98894496

00:41:45.150 --> 00:41:47.858 very tight location in the receptor.

NOTE Confidence: 0.98894496

00:41:47.858 --> 00:41:50.450 Then it stabilizes a conformational change

NOTE Confidence: 0.98894496

00:41:50.450 --> 00:41:54.685 of the receptor and this is communicated.

NOTE Confidence: 0.98894496

00:41:54.690 --> 00:41:58.278 From the outside of the cell.

NOTE Confidence: 0.98894496

00:41:58.280 --> 00:42:00.530 To the inside of the cell.

NOTE Confidence: 0.98894496

00:42:00.530 --> 00:42:02.960 Where the receptor here in white?

NOTE Confidence: 0.98894496

00:42:02.960 --> 00:42:04.860 Communicates with heterotrimeric G proteins

NOTE Confidence: 0.98894496

00:42:04.860 --> 00:42:07.970 and you'll see this is the G alpha subunit.

NOTE Confidence: 0.98894496

00:42:07.970 --> 00:42:10.388 This is the beta gamma subunit.

NOTE Confidence: 0.98894496

00:42:10.390 --> 00:42:13.295 They're now going to fly off and

NOTE Confidence: 0.98894496

00:42:13.295 --> 00:42:15.310 activate various downstream effectors.

NOTE Confidence: 0.98894496

00:42:15.310 --> 00:42:17.851 So the goal of my lab really

NOTE Confidence: 0.98894496

00:42:17.851 --> 00:42:19.830 for 30 years has been.

NOTE Confidence: 0.98894496

00:42:19.830 --> 00:42:22.582 To understand this process.

NOTE Confidence: 0.98894496

00:42:22.582 --> 00:42:23.270 And.

NOTE Confidence: 0.98894496

00:42:23.270 --> 00:42:26.216 We sort of understand it now.

NOTE Confidence: 0.98894496

00:42:26.220 --> 00:42:28.110 And the work,

NOTE Confidence: 0.98894496

00:42:28.110 --> 00:42:30.000 the real data that I'm going to

NOTE Confidence: 0.98894496

00:42:30.000 --> 00:42:32.252 show was developed by an extremely

NOTE Confidence: 0.98894496

00:42:32.252 --> 00:42:35.200 talented team of postdocs in my lab.

NOTE Confidence: 0.98894496

00:42:35.200 --> 00:42:37.072 Most all of whom now have their own labs.

NOTE Confidence: 0.98894496

00:42:37.080 --> 00:42:37.830 Shang, Tao,

NOTE Confidence: 0.98894496

00:42:37.830 --> 00:42:39.705 Daniel and John all have

NOTE Confidence: 0.98894496

00:42:39.705 --> 00:42:41.600 their own faculty positions.

NOTE Confidence: 0.98894496

00:42:41.600 --> 00:42:44.018 Brian Crum, still in the lab.

NOTE Confidence: 0.98894496

00:42:44.020 --> 00:42:46.678 If you're looking to hire someone,

NOTE Confidence: 0.98894496

00:42:46.680 --> 00:42:49.459 he'll be on the job market soon.

NOTE Confidence: 0.98894496

00:42:49.460 --> 00:42:50.082 Uhm,

NOTE Confidence: 0.98894496

00:42:50.082 --> 00:42:52.570 and so the first.

NOTE Confidence: 0.98894496

00:42:52.570 --> 00:42:55.026 The first finding was we were able to

NOTE Confidence: 0.98894496

00:42:55.026 --> 00:42:57.722 obtain the structure of LSD and complex

NOTE Confidence: 0.98894496

00:42:57.722 --> 00:42:59.737 with the human serotonin receptor.

NOTE Confidence: 0.98894496

00:42:59.740 --> 00:43:01.728 This was the five HT 2B receptor.

NOTE Confidence: 0.98894496

00:43:01.730 --> 00:43:03.818 It wasn't the two a 'cause we couldn't

NOTE Confidence: 0.98894496

00:43:03.820 --> 00:43:07.985 couldn't crystallize it with a two way.

NOTE Confidence: 0.98894496

00:43:07.990 --> 00:43:10.195 But it was important enough

NOTE Confidence: 0.98894496

00:43:10.195 --> 00:43:13.200 that it made the cover of sell,

NOTE Confidence: 0.98894496

00:43:13.200 --> 00:43:15.288 and to my delight,

NOTE Confidence: 0.98894496

00:43:15.288 --> 00:43:17.898 many of the predictions that

NOTE Confidence: 0.98894496

00:43:17.898 --> 00:43:19.804 we had made many,

NOTE Confidence: 0.98894496

00:43:19.804 --> 00:43:22.408 many years ago were verified once

NOTE Confidence: 0.98894496

00:43:22.408 --> 00:43:25.359 we had the crystal structure.

NOTE Confidence: 0.98912734

00:43:27.460 --> 00:43:30.100 And in particular,

NOTE Confidence: 0.98912734

00:43:30.100 --> 00:43:33.208 there were these two aromatic residues.

NOTE Confidence: 0.98912734

00:43:33.210 --> 00:43:36.588 These phenylalanine that we had predicted

NOTE Confidence: 0.98912734

00:43:36.590 --> 00:43:42.995 would stabilize the indole moiety of LSD

NOTE Confidence: 0.98912734

00:43:43.000 --> 00:43:46.857 and would be key to receptor recognition.

NOTE Confidence: 0.98912734

00:43:46.860 --> 00:43:50.500 And I was particularly happy to see this.

NOTE Confidence: 0.98912734

00:43:50.500 --> 00:43:54.760 Because, uh. In the early 1990s we

NOTE Confidence: 0.98912734

00:43:54.760 --> 00:43:57.116 had presented the data suggesting

NOTE Confidence: 0.98912734

00:43:57.116 --> 00:43:59.696 that these residues were involved.

NOTE Confidence: 0.98912734

00:43:59.700 --> 00:44:02.885 In psychedelic drug binding to the receptor,

NOTE Confidence: 0.98912734

00:44:02.890 --> 00:44:04.622 I remember presenting it

NOTE Confidence: 0.98912734

00:44:04.622 --> 00:44:06.354 at a neuroscience meeting.

NOTE Confidence: 0.98912734

00:44:06.360 --> 00:44:08.890 One of these short talks.

NOTE Confidence: 0.98912734

00:44:08.890 --> 00:44:11.356 There are a couple of 100 people in the

NOTE Confidence: 0.98912734

00:44:11.356 --> 00:44:13.235 audience and at the end of the talk.

NOTE Confidence: 0.98912734

00:44:13.240 --> 00:44:16.516 Uh, somebody who I won't mention who it is.

NOTE Confidence: 0.98912734

00:44:16.520 --> 00:44:19.761 Nobody from Yale stood up and said

NOTE Confidence: 0.98912734

00:44:19.761 --> 00:44:21.910 this cannot possibly be true.

NOTE Confidence: 0.98912734

00:44:21.910 --> 00:44:24.654 And a few weeks later my grant was

NOTE Confidence: 0.98912734

00:44:24.654 --> 00:44:28.499 reviewed and was was was nerfed.

NOTE Confidence: 0.98912734

00:44:28.500 --> 00:44:30.243 Nonetheless, we persisted,

NOTE Confidence: 0.98912734

00:44:30.243 --> 00:44:34.310 and it turned out we were correct.

NOTE Confidence: 0.98912734

00:44:34.310 --> 00:44:35.702 Uhm, the other.

NOTE Confidence: 0.98912734

00:44:35.702 --> 00:44:38.486 The other thing that we found

NOTE Confidence: 0.98912734

00:44:38.490 --> 00:44:41.030 with this receptor with this

NOTE Confidence: 0.98912734

00:44:41.030 --> 00:44:43.062 structure published in 2017,

NOTE Confidence: 0.98912734

00:44:43.070 --> 00:44:46.265 as well as finally we got the structure of

NOTE Confidence: 0.98912734

00:44:46.265 --> 00:44:49.557 LSD with the five HT 2A receptor in 2020.

NOTE Confidence: 0.98912734

00:44:49.560 --> 00:44:51.888 Was that there was a lid

NOTE Confidence: 0.98912734

00:44:51.888 --> 00:44:53.880 that was formed over LSD.

NOTE Confidence: 0.98912734

00:44:53.880 --> 00:44:57.060 By this loosening residue.

NOTE Confidence: 0.98912734

00:44:57.060 --> 00:45:02.120 And this lid basically falls.

NOTE Confidence: 0.98912734

00:45:02.120 --> 00:45:04.640 Fits over the top of LSD so that LSD

NOTE Confidence: 0.98912734

00:45:04.640 --> 00:45:06.717 can't get out of their receptor.

NOTE Confidence: 0.98912734

00:45:06.720 --> 00:45:08.290 And and because of this,

NOTE Confidence: 0.98912734

00:45:08.290 --> 00:45:09.916 LSD is a very long residence

NOTE Confidence: 0.98912734

00:45:09.916 --> 00:45:11.000 time in the receptor.

NOTE Confidence: 0.98912734

00:45:11.000 --> 00:45:13.135 Basically once LSD is on the receptor,

NOTE Confidence: 0.98912734

00:45:13.140 --> 00:45:16.570 it's there for two to three hours at least,

NOTE Confidence: 0.98912734

00:45:16.570 --> 00:45:19.570 and this explains in large part

NOTE Confidence: 0.98912734

00:45:19.570 --> 00:45:23.229 why LSD actions are so prolonged.

NOTE Confidence: 0.98912734

00:45:23.230 --> 00:45:27.424 Jor Rhonda Ross Lab did molecular

NOTE Confidence: 0.98912734

00:45:27.424 --> 00:45:30.220 dynamics simulations of this,

NOTE Confidence: 0.98912734

00:45:30.220 --> 00:45:34.271 and this is an MD simulation of

NOTE Confidence: 0.98912734

00:45:34.271 --> 00:45:36.857 LSD with the native receptor here,

NOTE Confidence: 0.98912734

00:45:36.860 --> 00:45:38.701 and you can see this leucine here

NOTE Confidence: 0.98912734

00:45:38.701 --> 00:45:40.766 and you can see LSD is pretty

NOTE Confidence: 0.98912734

00:45:40.766 --> 00:45:42.590 stable here in the binding pocket.

NOTE Confidence: 0.98912734

00:45:42.590 --> 00:45:44.590 When the leucine was changed to an alanine,

NOTE Confidence: 0.98912734

00:45:44.590 --> 00:45:47.587 we can see that LSD is now moving around.

NOTE Confidence: 0.98912734

00:45:47.590 --> 00:45:49.970 A bit more begins to actually float

NOTE Confidence: 0.98912734

00:45:49.970 --> 00:45:53.690 out of the binding pocket and we are

NOTE Confidence: 0.98912734

00:45:53.690 --> 00:46:00.070 able to show by biophysical studies that.

NOTE Confidence: 0.98912734

00:46:00.070 --> 00:46:01.194 Mutants, uh?

NOTE Confidence: 0.98912734

00:46:01.194 --> 00:46:04.004 Of this of this residue,

NOTE Confidence: 0.98912734

00:46:04.010 --> 00:46:05.780 greatly accelerate the off time

NOTE Confidence: 0.98912734

00:46:05.780 --> 00:46:07.550 of LSD from the receptor,

NOTE Confidence: 0.98912734

00:46:07.550 --> 00:46:11.576 so we think this is key for LSD's actions.

NOTE Confidence: 0.98912734

00:46:11.576 --> 00:46:14.430 Uhm? The other big advance was.

NOTE Confidence: 0.936355556

00:46:17.190 --> 00:46:20.300 Obtaining by cryo electron microscopy.

NOTE Confidence: 0.936355556

00:46:20.300 --> 00:46:23.429 The structure of the five HT 2A

NOTE Confidence: 0.936355556

00:46:23.429 --> 00:46:25.970 receptor bound to a psychedelic drug

NOTE Confidence: 0.936355556

00:46:25.970 --> 00:46:28.451 and bound to the heterotrimeric G

NOTE Confidence: 0.936355556

00:46:28.451 --> 00:46:31.512 protein GI thank you and this is a

NOTE Confidence: 0.936355556

00:46:31.512 --> 00:46:34.230 study that was done principally by

NOTE Confidence: 0.936355556

00:46:34.325 --> 00:46:37.426 KU from my lab and Julianna Pena

NOTE Confidence: 0.936355556

00:46:37.426 --> 00:46:40.650 over from your Goscinny Ellis lab.

NOTE Confidence: 0.936355556

00:46:40.650 --> 00:46:42.600 To cry OEM Soku basically did

NOTE Confidence: 0.936355556

00:46:42.600 --> 00:46:43.900 all the biochemical studies,

NOTE Confidence: 0.936355556

00:46:43.900 --> 00:46:45.846 purify the receptor, send it to them.

NOTE Confidence: 0.936355556

00:46:45.850 --> 00:46:48.418 They solved the structure.

NOTE Confidence: 0.936355556

00:46:48.420 --> 00:46:50.160 And I'm just going to show

NOTE Confidence: 0.936355556

00:46:50.160 --> 00:46:51.320 you some details here.

NOTE Confidence: 0.936355556

00:46:51.320 --> 00:46:54.328 Here you can see this psychedelic drug 25

NOTE Confidence: 0.936355556

00:46:54.328 --> 00:46:57.365 sayano in Bo bound to the receptor here.

NOTE Confidence: 0.981994538333333

00:47:00.060 --> 00:47:02.958 This is a space filling representation.

NOTE Confidence: 0.981994538333333

00:47:02.960 --> 00:47:04.745 Uh, we're going to zoom up on

NOTE Confidence: 0.981994538333333

00:47:04.745 --> 00:47:06.759 the the G protein interface.

NOTE Confidence: 0.981994538333333

00:47:06.760 --> 00:47:09.728 The alpha subunit there is in blue.

NOTE Confidence: 0.981994538333333

00:47:09.730 --> 00:47:11.166 Uhm, there's the receptor.

NOTE Confidence: 0.981994538333333

00:47:11.166 --> 00:47:13.730 You can see that with this drug.

NOTE Confidence: 0.981994538333333

00:47:13.730 --> 00:47:16.796 The binding pocket is relatively open.

NOTE Confidence: 0.981994538333333

00:47:16.800 --> 00:47:21.784 Uh, there is the drug is in yellow.

NOTE Confidence: 0.981994538333333

00:47:21.790 --> 00:47:24.460 And, uh.

NOTE Confidence: 0.981994538333333

00:47:24.460 --> 00:47:27.068 And it has a sort of really interesting

NOTE Confidence: 0.981994538333333

00:47:27.068 --> 00:47:29.879 mode of interaction with the receptor,

NOTE Confidence: 0.981994538333333

00:47:29.880 --> 00:47:31.896 which I I'm not going to go in today,

NOTE Confidence: 0.981994538333333

00:47:31.900 --> 00:47:34.910 so this this was really a breakthrough.

NOTE Confidence: 0.981994538333333

00:47:34.910 --> 00:47:39.870 This is actually discovering.

NOTE Confidence: 0.981994538333333

00:47:39.870 --> 00:47:41.544 Psychedelic drug action

NOTE Confidence: 0.981994538333333

00:47:41.544 --> 00:47:43.776 at the molecular level.

NOTE Confidence: 0.981994538333333

00:47:43.780 --> 00:47:47.357 And along with this active state structure,

NOTE Confidence: 0.981994538333333

00:47:47.360 --> 00:47:50.125 we were able to obtain inactive state

NOTE Confidence: 0.981994538333333

00:47:50.125 --> 00:47:52.878 structures of the five HT 2A receptor,

NOTE Confidence: 0.981994538333333

00:47:52.880 --> 00:47:55.365 and this allowed us to map the

NOTE Confidence: 0.981994538333333

00:47:55.365 --> 00:47:56.893 transitions that occur between

NOTE Confidence: 0.981994538333333

00:47:56.893 --> 00:47:59.245 the active in the inactive state.

NOTE Confidence: 0.981994538333333

00:47:59.250 --> 00:48:00.286 And they're shown here,

NOTE Confidence: 0.981994538333333

00:48:00.286 --> 00:48:01.840 and I'm not going to go

NOTE Confidence: 0.981994538333333

00:48:01.903 --> 00:48:03.445 into any of these in detail.

NOTE Confidence: 0.981994538333333

00:48:03.450 --> 00:48:06.649 There only probably one or two structural

NOTE Confidence: 0.981994538333333

00:48:06.649 --> 00:48:08.524 biologists here in the audience.

NOTE Confidence: 0.981994538333333

00:48:08.524 --> 00:48:11.390 But just to let you know that it gives

NOTE Confidence: 0.981994538333333

00:48:11.390 --> 00:48:13.310 us great insight into into basically

NOTE Confidence: 0.981994538333333

00:48:13.310 --> 00:48:15.298 how drugs activate the receptor.

NOTE Confidence: 0.987948635555556

00:48:18.030 --> 00:48:20.802 I'm now going to show some some new data.

NOTE Confidence: 0.987948635555556

00:48:20.810 --> 00:48:23.780 Uh, and this is some amazing

NOTE Confidence: 0.987948635555556

00:48:23.780 --> 00:48:26.794 data that has has recently been

NOTE Confidence: 0.987948635555556

00:48:26.794 --> 00:48:28.542 prepared by an extraordinarily

NOTE Confidence: 0.987948635555556

00:48:28.542 --> 00:48:30.526 talented postdoc at mine, Ryan,

NOTE Confidence: 0.987948635555556

00:48:30.526 --> 00:48:33.106 in collaboration with Jonathan Fay,

NOTE Confidence: 0.987948635555556

00:48:33.110 --> 00:48:35.925 who's the local cry OEM

NOTE Confidence: 0.987948635555556

00:48:35.925 --> 00:48:39.320 wizard here at at UNC and.

NOTE Confidence: 0.9860263525

00:48:41.930 --> 00:48:46.216 Collectively, over the last year or so,

NOTE Confidence: 0.9860263525

00:48:46.216 --> 00:48:48.400 they've been able to obtain a large

NOTE Confidence: 0.9860263525

00:48:48.471 --> 00:48:51.920 number of structures of the five HT 2A

NOTE Confidence: 0.9860263525

00:48:51.920 --> 00:48:54.040 receptor and another serotonin receptors

NOTE Confidence: 0.9860263525

71

00:48:54.122 --> 00:48:56.506 related serotonin receptors with

NOTE Confidence: 0.9860263525

00:48:56.506 --> 00:48:58.536 psychedelic and on psychedelic drugs.

NOTE Confidence: 0.9860263525

00:48:58.540 --> 00:48:59.596 So I'm not going to go into any

NOTE Confidence: 0.9860263525

00:48:59.596 --> 00:49:00.598 of these structures in detail,

NOTE Confidence: 0.9860263525

00:49:00.600 --> 00:49:01.848 but just to let you know,

NOTE Confidence: 0.9860263525

00:49:01.850 --> 00:49:03.915 we now have the structure of mescalin.

NOTE Confidence: 0.9860263525

00:49:03.920 --> 00:49:05.460 We have the structure of

NOTE Confidence: 0.9860263525

00:49:05.460 --> 00:49:06.254 NN Dimethyltryptamine.

NOTE Confidence: 0.9860263525

00:49:06.254 --> 00:49:08.636 We have the structure of psilocin.

NOTE Confidence: 0.9860263525

00:49:08.640 --> 00:49:10.700 So basically all major psychedelics

NOTE Confidence: 0.9860263525

00:49:10.700 --> 00:49:12.348 we have structures of.

NOTE Confidence: 0.9860263525

00:49:12.350 --> 00:49:15.086 We also have structures of the

NOTE Confidence: 0.9860263525

00:49:15.086 --> 00:49:16.910 non psychedelic compounds blsa

NOTE Confidence: 0.9860263525

00:49:16.993 --> 00:49:18.938 ride as well as serotonin,

NOTE Confidence: 0.9860263525

00:49:18.940 --> 00:49:21.484 and we're using these structures for

NOTE Confidence: 0.9860263525

00:49:21.484 --> 00:49:23.180 structure guided drug discovery,

NOTE Confidence: 0.9860263525

00:49:23.180 --> 00:49:26.562 which I'll I'll go over here

NOTE Confidence: 0.9860263525

00:49:26.562 --> 00:49:28.154 in just a minute.

NOTE Confidence: 0.9860263525

00:49:28.160 --> 00:49:31.841 Uhm, now one of the other things that we

NOTE Confidence: 0.9860263525

00:49:31.841 --> 00:49:34.896 noticed about about LSD in particular.

NOTE Confidence: 0.9860263525

00:49:34.900 --> 00:49:37.438 Uh, and if you remember I I said early

NOTE Confidence: 0.9860263525

00:49:37.438 --> 00:49:40.451 on that five HT 2A receptors not only

NOTE Confidence: 0.9860263525

00:49:40.451 --> 00:49:43.180 activate this geovic you signaling pathway,

NOTE Confidence: 0.9860263525

00:49:43.180 --> 00:49:46.170 they also activated arrestin signaling.

NOTE Confidence: 0.9860263525

00:49:46.170 --> 00:49:49.010 What we found was that if we did

NOTE Confidence: 0.9860263525

00:49:49.010 --> 00:49:51.228 dose response studies looking at

NOTE Confidence: 0.9860263525

00:49:51.228 --> 00:49:53.892 the ability of LSD to activate

NOTE Confidence: 0.9860263525

00:49:53.892 --> 00:49:55.639 arrestin versus gioffre Q,

NOTE Confidence: 0.9860263525

00:49:55.640 --> 00:49:57.912 we found that it was much much more

NOTE Confidence: 0.9860263525

00:49:57.912 --> 00:50:01.194 potent for activating arrested the GL.

NOTE Confidence: 0.9860263525

00:50:01.194 --> 00:50:02.668 Thank you.

NOTE Confidence: 0.9860263525

73

00:50:02.670 --> 00:50:06.585 And this led led to the idea that LSD,

NOTE Confidence: 0.9860263525

00:50:06.590 --> 00:50:11.570 maybe an arrest in biased ligand for

NOTE Confidence: 0.9860263525

00:50:11.570 --> 00:50:15.410 the serotonin receptor and that that

NOTE Confidence: 0.9860263525

00:50:15.410 --> 00:50:18.914 this might be responsible, at least in part.

NOTE Confidence: 0.9860263525

00:50:18.914 --> 00:50:22.030 For some of the actions of LSD.

NOTE Confidence: 0.9860263525

00:50:22.030 --> 00:50:25.120 And so to begin to.

NOTE Confidence: 0.9860263525

00:50:25.120 --> 00:50:27.372 But test this hypothesis.

NOTE Confidence: 0.9860263525

00:50:27.372 --> 00:50:28.498 This is,

NOTE Confidence: 0.9860263525

00:50:28.500 --> 00:50:30.112 this was recently published.

NOTE Confidence: 0.9860263525

00:50:30.112 --> 00:50:33.821 This was a study that was done by Ramona

NOTE Confidence: 0.9860263525

00:50:33.821 --> 00:50:36.642 Rodriguez in Bill Wetzel's Lab at Duke.

NOTE Confidence: 0.9860263525

00:50:36.650 --> 00:50:39.303 They evaluated the ability of LSD to

NOTE Confidence: 0.9860263525

00:50:39.303 --> 00:50:42.038 induce head Twitch response in wild

NOTE Confidence: 0.9860263525

00:50:42.038 --> 00:50:44.942 type mice versus beta arrestin 2

NOTE Confidence: 0.9860263525

00:50:44.942 --> 00:50:47.807 knockout mice and to make a Long story short,

NOTE Confidence: 0.9860263525

00:50:47.810 --> 00:50:51.159 what they found was that of course LSD

NOTE Confidence: 0.9860263525

00:50:51.159 --> 00:50:54.057 induces head Twitch response very robustly.

NOTE Confidence: 0.9860263525

00:50:54.060 --> 00:50:56.356 This response can be blocked by a

NOTE Confidence: 0.9860263525

00:50:56.356 --> 00:50:59.356 five HT 2 antagonist and 109 oh,

NOTE Confidence: 0.9860263525

00:50:59.356 --> 00:51:01.708 seven and that this response is

NOTE Confidence: 0.9860263525

00:51:01.708 --> 00:51:04.602 greatly attenuated in beta arrestin 2

NOTE Confidence: 0.9860263525

00:51:04.602 --> 00:51:07.550 but not beta arrestin one knockout mice.

NOTE Confidence: 0.9860263525

00:51:07.550 --> 00:51:07.996 Uhm,

NOTE Confidence: 0.9860263525

00:51:07.996 --> 00:51:11.564 and as well a number of other sort

NOTE Confidence: 0.9860263525

00:51:11.564 --> 00:51:15.182 of classic effects of psychedelic

NOTE Confidence: 0.9860263525

00:51:15.182 --> 00:51:19.705 drugs on mouse phenotypes were also

NOTE Confidence: 0.9860263525

00:51:19.705 --> 00:51:21.492 attenuated in the bait arrested.

NOTE Confidence: 0.9860263525

00:51:21.492 --> 00:51:22.266 Two knockout mice.

NOTE Confidence: 0.9860263525

00:51:22.270 --> 00:51:24.277 One of the ones that I like to highlight

NOTE Confidence: 0.9860263525

00:51:24.277 --> 00:51:26.590 is this disruption of prepulse inhibition.

NOTE Confidence: 0.9860263525

00:51:26.590 --> 00:51:29.290 You can see that LSD greatly

NOTE Confidence: 0.9860263525

00:51:29.290 --> 00:51:31.090 disrupts prepulse inhibition here,

NOTE Confidence: 0.9860263525

00:51:31.090 --> 00:51:34.640 but there is no effect.

NOTE Confidence: 0.9860263525

00:51:34.640 --> 00:51:35.622 In debate,

NOTE Confidence: 0.9860263525

00:51:35.622 --> 00:51:38.902 arrested two knockout mice and because

NOTE Confidence: 0.9860263525

00:51:38.902 --> 00:51:42.838 LSD disrupts prepulse inhibition in both.

NOTE Confidence: 0.9860263525

00:51:42.840 --> 00:51:44.691 Mice and humans?

NOTE Confidence: 0.9860263525

00:51:44.691 --> 00:51:45.308 Uh,

NOTE Confidence: 0.9860263525

00:51:45.308 --> 00:51:48.393 this is potentially a translational

NOTE Confidence: 0.9860263525

00:51:48.393 --> 00:51:51.770 biomarker going forward for investigating

NOTE Confidence: 0.9860263525

00:51:51.770 --> 00:51:55.095 the psychoactive effects of LSD,

NOTE Confidence: 0.9860263525

00:51:55.100 --> 00:51:57.540 as distinct from potentially novel

NOTE Confidence: 0.9860263525

00:51:57.540 --> 00:52:01.200 drugs that may not be psychoactive.

NOTE Confidence: 0.9860263525

00:52:01.200 --> 00:52:03.084 Uhm, as I mentioned,

NOTE Confidence: 0.9860263525

00:52:03.084 --> 00:52:05.492 we have a we have been creating

NOTE Confidence: 0.9860263525

00:52:05.492 --> 00:52:06.484 a number of mice.

NOTE Confidence: 0.9860263525

00:52:06.490 --> 00:52:07.698 UM, we.

NOTE Confidence: 0.9860263525

00:52:07.698 --> 00:52:11.926 To study this in in more detail

NOTE Confidence: 0.9860263525

00:52:11.926 --> 00:52:14.270 and I just want to mention,

NOTE Confidence: 0.9860263525

00:52:14.270 --> 00:52:14.723 uh,

NOTE Confidence: 0.9860263525

00:52:14.723 --> 00:52:17.894 there are five HT 2A cream ists

NOTE Confidence: 0.9860263525

00:52:17.894 --> 00:52:21.488 that are available through gensac.

NOTE Confidence: 0.9860263525

00:52:21.490 --> 00:52:23.706 I would urge you not to use those

NOTE Confidence: 0.9860263525

00:52:23.706 --> 00:52:26.400 mice because the cells that are

NOTE Confidence: 0.9860263525

00:52:26.400 --> 00:52:28.810 labeled by creari combinations are

NOTE Confidence: 0.950371805

00:52:28.896 --> 00:52:30.871 not five HT 2A expressing

NOTE Confidence: 0.950371805

00:52:30.871 --> 00:52:33.038 mice 5 HT 2A receptors.

NOTE Confidence: 0.950371805

00:52:33.038 --> 00:52:36.828 We found this out some years ago and because

NOTE Confidence: 0.950371805

00:52:36.828 --> 00:52:39.860 of that went to the trouble to create.

NOTE Confidence: 0.950371805

00:52:39.860 --> 00:52:42.817 Uh, our own set of mice using

NOTE Confidence: 0.950371805

00:52:42.817 --> 00:52:43.951 CRISPR technology.

NOTE Confidence: 0.950371805

00:52:43.951 --> 00:52:48.210 And I'll just show you results from 1.

NOTE Confidence: 0.950371805

00:52:48.210 --> 00:52:50.685 One of the various types of mice we've made,

NOTE Confidence: 0.950371805

00:52:50.690 --> 00:52:53.345 this is a mouse in which the five HT

NOTE Confidence: 0.950371805

00:52:53.345 --> 00:52:55.859 2A receptor has been tagged with GFP

NOTE Confidence: 0.950371805

00:52:55.859 --> 00:52:59.718 in such a way that it does not affect

NOTE Confidence: 0.950371805

00:52:59.718 --> 00:53:01.602 receptor expression or function.

NOTE Confidence: 0.950371805

00:53:01.610 --> 00:53:04.389 And then downstream of that 'cause pirates

NOTE Confidence: 0.950371805

00:53:04.389 --> 00:53:07.529 and then a estrogen responsive Cree.

NOTE Confidence: 0.950371805

00:53:07.530 --> 00:53:09.774 And you can see here from

NOTE Confidence: 0.950371805

00:53:09.774 --> 00:53:11.270 this sagittal section here,

NOTE Confidence: 0.950371805

00:53:11.270 --> 00:53:13.748 that the distribution of five HT 2A

NOTE Confidence: 0.950371805

00:53:13.748 --> 00:53:16.100 receptor protein is virtually identical

NOTE Confidence: 0.950371805

00:53:16.100 --> 00:53:19.894 to that which was identified by receptor

NOTE Confidence: 0.950371805

00:53:19.894 --> 00:53:22.108 autoradiography with M109O7 many,

NOTE Confidence: 0.950371805

00:53:22.108 --> 00:53:26.000 many years ago by the Palacios lab.

NOTE Confidence: 0.950371805

00:53:26.000 --> 00:53:28.680 I also want to point out this patchy

NOTE Confidence: 0.950371805

00:53:28.680 --> 00:53:30.935 distribution here in the striatum

NOTE Confidence: 0.950371805

00:53:30.935 --> 00:53:33.656 which which is sort of hinted

NOTE Confidence: 0.950371805

00:53:33.656 --> 00:53:35.589 at here in this autoradiogram.

NOTE Confidence: 0.950371805

00:53:35.589 --> 00:53:37.554 But the resolution is just

NOTE Confidence: 0.950371805

00:53:37.554 --> 00:53:39.020 not sufficient to see it.

NOTE Confidence: 0.950371805

00:53:39.020 --> 00:53:40.760 So we think there are some.

NOTE Confidence: 0.950371805

00:53:40.760 --> 00:53:42.048 There's some interesting activity

NOTE Confidence: 0.950371805

00:53:42.048 --> 00:53:43.336 here in this trisome,

NOTE Confidence: 0.950371805

00:53:43.340 --> 00:53:46.094 but the key thing here is these layer 5

NOTE Confidence: 0.950371805

00:53:46.094 --> 00:53:48.428 neurons are just really really lit up.

NOTE Confidence: 0.950371805

00:53:48.430 --> 00:53:51.478 And and so we we crossed these five

NOTE Confidence: 0.950371805

00:53:51.478 --> 00:53:55.151 HT 2A estrogen responsive Cree with

NOTE Confidence: 0.950371805

00:53:55.151 --> 00:53:58.637 Phlox beta arrestin 2 knockout mice.

NOTE Confidence: 0.950371805

00:53:58.640 --> 00:54:01.388 Treated them with tamoxifen.

NOTE Confidence: 0.950371805

00:54:01.390 --> 00:54:04.344 And then evaluated the ability of LSD

NOTE Confidence: 0.950371805

00:54:04.350 --> 00:54:06.708 and DOB to induce hedgewitch response.

NOTE Confidence: 0.950371805

00:54:06.710 --> 00:54:08.684 And you can see in both cases

NOTE Confidence: 0.950371805

00:54:08.690 --> 00:54:10.370 the effect was attenuated.

NOTE Confidence: 0.950371805

00:54:10.370 --> 00:54:11.210 It's not.

NOTE Confidence: 0.950371805

00:54:11.210 --> 00:54:12.401 It's not abolished,

NOTE Confidence: 0.950371805

00:54:12.401 --> 00:54:13.989 but it's attenuated again,

NOTE Confidence: 0.950371805

00:54:13.990 --> 00:54:16.140 suggesting that there might be

NOTE Confidence: 0.950371805

00:54:16.140 --> 00:54:18.654 some role for beta arrestin in

NOTE Confidence: 0.950371805

00:54:18.654 --> 00:54:20.110 addition to GQ signaling,

NOTE Confidence: 0.950371805

00:54:20.110 --> 00:54:23.660 for for mediating the effects of

NOTE Confidence: 0.950371805

00:54:23.660 --> 00:54:25.520 psychedelics at the molecular basis.

NOTE Confidence: 0.950371805

00:54:25.520 --> 00:54:25.851 OK,

NOTE Confidence: 0.950371805

00:54:25.851 --> 00:54:28.254 I want to finish now with with

NOTE Confidence: 0.950371805

00:54:28.254 --> 00:54:30.738 some very recent studies which are

NOTE Confidence: 0.950371805

00:54:30.738 --> 00:54:32.964 currently in review which were done

NOTE Confidence: 0.950371805

00:54:32.964 --> 00:54:34.932 in collaboration with the Ellen Lab

NOTE Confidence: 0.950371805

00:54:34.932 --> 00:54:37.673 here at Yale University by a very

NOTE Confidence: 0.950371805

00:54:37.673 --> 00:54:40.259 talented student of his Denise Confair.

NOTE Confidence: 0.950371805

00:54:40.260 --> 00:54:41.920 In collaboration with my lab,

NOTE Confidence: 0.950371805

00:54:41.920 --> 00:54:43.270 the Irwin Lab at UCSF,

NOTE Confidence: 0.950371805

00:54:43.270 --> 00:54:48.190 and the Shortcut Lab at at at UCSF.

NOTE Confidence: 0.950371805

00:54:48.190 --> 00:54:48.708 And,

NOTE Confidence: 0.950371805

00:54:48.708 --> 00:54:49.226 uh,

NOTE Confidence: 0.950371805

00:54:49.226 --> 00:54:53.385 what was done here was now that we had

NOTE Confidence: 0.950371805

00:54:53.385 --> 00:54:57.076 the structure of the five HT 2A receptor.

NOTE Confidence: 0.950371805

00:54:57.080 --> 00:55:00.256 We wondered if we could use it for

NOTE Confidence: 0.950371805

00:55:00.256 --> 00:55:02.319 structure based drug discovery.

NOTE Confidence: 0.950371805

00:55:02.320 --> 00:55:05.743 And in the past the Choquette Irwin

NOTE Confidence: 0.950371805

00:55:05.743 --> 00:55:09.024 lab in my lab have published a number

NOTE Confidence: 0.950371805

00:55:09.024 --> 00:55:10.692 of studies where we've done what

NOTE Confidence: 0.950371805

00:55:10.692 --> 00:55:12.618 we call ultra large scale docking,

NOTE Confidence: 0.950371805

00:55:12.620 --> 00:55:15.772 where large numbers of commercially

NOTE Confidence: 0.950371805

00:55:15.772 --> 00:55:17.940 available compounds are docked

NOTE Confidence: 0.950371805

00:55:17.940 --> 00:55:19.940 to a receptor structure,

NOTE Confidence: 0.950371805

00:55:19.940 --> 00:55:23.344 and then they eventually become seed

NOTE Confidence: 0.950371805

00:55:23.344 --> 00:55:26.349 compounds for medicinal chemistry efforts.

NOTE Confidence: 0.950371805

00:55:26.350 --> 00:55:26.708 Now,

NOTE Confidence: 0.950371805

00:55:26.708 --> 00:55:29.214 one of the problems with using these

NOTE Confidence: 0.950371805

00:55:29.214 --> 00:55:30.922 commercially available libraries is

NOTE Confidence: 0.950371805

00:55:30.922 --> 00:55:32.786 they're they're relatively congested.

NOTE Confidence: 0.950371805

00:55:32.790 --> 00:55:35.780 In terms of chemical space.

NOTE Confidence: 0.950371805

00:55:35.780 --> 00:55:38.092 And one of the one of the areas

NOTE Confidence: 0.950371805

00:55:38.092 --> 00:55:40.516 of chemical space which are

NOTE Confidence: 0.950371805

00:55:40.516 --> 00:55:41.700 relatively underrepresented,

NOTE Confidence: 0.950371805

00:55:41.700 --> 00:55:43.820 underrepresented in these large

NOTE Confidence: 0.950371805

00:55:43.820 --> 00:55:45.940 libraries are tetrahydro purities.

NOTE Confidence: 0.950371805

00:55:45.940 --> 00:55:49.756 And so Jonathan Elman really is a wizard at

NOTE Confidence: 0.950371805

00:55:49.760 --> 00:55:53.936 at sort of diversity oriented synthesis.

NOTE Confidence: 0.950371805

00:55:53.940 --> 00:55:56.286 And so he and Denise had.

NOTE Confidence: 0.950371805

00:55:56.290 --> 00:55:56.723 Uhm,

NOTE Confidence: 0.950371805

00:55:56.723 --> 00:55:59.321 envisioned a way in which a

NOTE Confidence: 0.950371805

00:55:59.321 --> 00:56:01.144 large virtual tetrahydro purity

NOTE Confidence: 0.950371805

00:56:01.144 --> 00:56:02.908 library could be made.

NOTE Confidence: 0.986374247777778

00:56:02.910 --> 00:56:06.384 So this is a library that exists in theory,

NOTE Confidence: 0.986374247777778

00:56:06.390 --> 00:56:08.505 whereby relatively simple

NOTE Confidence: 0.986374247777778

00:56:08.505 --> 00:56:11.325 building blocks can be.

NOTE Confidence: 0.986374247777778

00:56:11.330 --> 00:56:13.414 Combine to make large,

NOTE Confidence: 0.986374247777778

00:56:13.414 --> 00:56:15.498 potentially large chemical libraries.

NOTE Confidence: 0.986374247777778

00:56:15.500 --> 00:56:19.220 In this case. This is a library of.

NOTE Confidence: 0.986374247777778

00:56:19.220 --> 00:56:22.470 75 million virtual tetrahydro purities.

NOTE Confidence: 0.986374247777778

00:56:22.470 --> 00:56:25.676 And what was done then is this

NOTE Confidence: 0.986374247777778

00:56:25.676 --> 00:56:28.004 was then docked to the receptor,

NOTE Confidence: 0.986374247777778

00:56:28.004 --> 00:56:29.912 and then an iterative cycle of

NOTE Confidence: 0.986374247777778

00:56:29.912 --> 00:56:31.757 docking and synthetic collaboration

NOTE Confidence: 0.986374247777778

00:56:31.757 --> 00:56:33.709 and optimization was performed.

NOTE Confidence: 0.986374247777778

00:56:33.710 --> 00:56:35.046 And ultimately,

NOTE Confidence: 0.986374247777778

00:56:35.046 --> 00:56:38.505 this compound 3366 was revealed as

NOTE Confidence: 0.986374247777778

00:56:38.505 --> 00:56:40.930 a relatively potent and selective,

NOTE Confidence: 0.986374247777778

00:56:40.930 --> 00:56:45.388 and importantly, GQ biased 5HT2 agonist.

NOTE Confidence: 0.986374247777778

00:56:45.390 --> 00:56:47.665 And the approach that was used has

NOTE Confidence: 0.986374247777778

00:56:47.665 --> 00:56:49.433 been described previously and I just

NOTE Confidence: 0.986374247777778

00:56:49.433 --> 00:56:51.141 want to point out these two papers

NOTE Confidence: 0.986374247777778

00:56:51.198 --> 00:56:52.906 that will be coming out in nature

NOTE Confidence: 0.986374247777778

00:56:52.906 --> 00:56:55.228 here in the next month where this

NOTE Confidence: 0.986374247777778

00:56:55.228 --> 00:56:57.610 was done on other other targets.

NOTE Confidence: 0.986374247777778

00:56:57.610 --> 00:56:59.297 Uhm, and so the way the docking

NOTE Confidence: 0.986374247777778

00:56:59.297 --> 00:57:00.370 is done is this.

NOTE Confidence: 0.986374247777778

00:57:00.370 --> 00:57:03.498 So each ligand separately is

NOTE Confidence: 0.986374247777778

00:57:03.498 --> 00:57:05.086 docked in multiple confirmations

NOTE Confidence: 0.986374247777778

00:57:05.086 --> 00:57:07.090 and you can see that there,

NOTE Confidence: 0.986374247777778

00:57:07.090 --> 00:57:09.910 and for each confirmation

NOTE Confidence: 0.986374247777778

00:57:09.910 --> 00:57:12.025 score is calculated.

NOTE Confidence: 0.986374247777778

00:57:12.030 --> 00:57:13.962 So you can see them docked

NOTE Confidence: 0.986374247777778

00:57:13.962 --> 00:57:16.160 and the score is calculated.

NOTE Confidence: 0.986374247777778

00:57:16.160 --> 00:57:17.206 And then,

NOTE Confidence: 0.986374247777778

00:57:17.206 --> 00:57:17.729 uhm.

NOTE Confidence: 0.985358815294118

00:57:19.860 --> 00:57:21.967 The Top Rank scores chosen for each

NOTE Confidence: 0.985358815294118

00:57:21.967 --> 00:57:23.940 of the hundreds of millions of

NOTE Confidence: 0.985358815294118

00:57:23.940 --> 00:57:27.040 compounds that are docked and then

NOTE Confidence: 0.985358815294118

00:57:27.040 --> 00:57:29.330 all the compounds are ranked and

NOTE Confidence: 0.985358815294118

00:57:29.330 --> 00:57:33.530 then a subset of them were tested.

NOTE Confidence: 0.985358815294118

00:57:33.530 --> 00:57:36.085 Uh, and ultimately optimized to

NOTE Confidence: 0.985358815294118

00:57:36.085 --> 00:57:38.691 this very potent compound 3366.

NOTE Confidence: 0.985358815294118

00:57:38.691 --> 00:57:43.312 So we had this compound 3366 we had

NOTE Confidence: 0.985358815294118

85

00:57:43.312 --> 00:57:46.936 predicted based on our computational studies,

NOTE Confidence: 0.985358815294118

00:57:46.940 --> 00:57:48.515 how it might bind to the receptor.

NOTE Confidence: 0.985358815294118

00:57:48.520 --> 00:57:50.856 We found that it bound to the receptor.

NOTE Confidence: 0.985358815294118

00:57:50.860 --> 00:57:53.471 We wanted to determine if our predictions

NOTE Confidence: 0.985358815294118

00:57:53.471 --> 00:57:57.030 were correct and so we enlisted the

NOTE Confidence: 0.985358815294118

00:57:57.030 --> 00:57:59.278 assistance of our collaborator,

NOTE Confidence: 0.985358815294118

00:57:59.280 --> 00:58:01.810 Jargo Skinny Otis at Stanford,

NOTE Confidence: 0.985358815294118

00:58:01.810 --> 00:58:04.000 and this really talented postdoc

NOTE Confidence: 0.985358815294118

00:58:04.000 --> 00:58:04.876 Cometa Barrows.

NOTE Confidence: 0.985358815294118

00:58:04.880 --> 00:58:09.668 Alvarez, who's now in the biotech industry.

NOTE Confidence: 0.985358815294118

00:58:09.670 --> 00:58:12.618 And they perform cry OEM elucidation

NOTE Confidence: 0.985358815294118

00:58:12.618 --> 00:58:16.524 of the structure of this this new

NOTE Confidence: 0.985358815294118

00:58:16.524 --> 00:58:19.917 compound with the five HT 2A receptor

NOTE Confidence: 0.985358815294118

00:58:19.920 --> 00:58:23.456 and what you can see here in green is

NOTE Confidence: 0.985358815294118

00:58:23.456 --> 00:58:25.832 the predicted pose of the compound

NOTE Confidence: 0.985358815294118

00:58:25.832 --> 00:58:28.211 in the receptor and in purple.

NOTE Confidence: 0.985358815294118

00:58:28.211 --> 00:58:30.990 Here is actually the solved pose by

NOTE Confidence: 0.985358815294118

00:58:31.073 --> 00:58:34.168 cryo electron microscopy and you can

NOTE Confidence: 0.985358815294118

00:58:34.168 --> 00:58:36.940 see that it was pretty close actually.

NOTE Confidence: 0.985358815294118

00:58:36.940 --> 00:58:39.768 So the cryo EM structure superposes quite.

NOTE Confidence: 0.985358815294118

00:58:39.770 --> 00:58:43.420 Well, with a computational prediction.

NOTE Confidence: 0.985358815294118

00:58:43.420 --> 00:58:43.996 Uhm,

NOTE Confidence: 0.985358815294118

00:58:43.996 --> 00:58:48.604 we tested the compounds for 4G protein bias,

NOTE Confidence: 0.985358815294118

00:58:48.610 --> 00:58:49.530 which you can see here.

NOTE Confidence: 0.985358815294118

00:58:49.530 --> 00:58:50.726 They're they're fairly biased.

NOTE Confidence: 0.985358815294118

00:58:50.726 --> 00:58:53.608 I'm not going to go into that in any detail.

NOTE Confidence: 0.985358815294118

00:58:53.610 --> 00:58:56.417 We also tested the drug like properties

NOTE Confidence: 0.985358815294118

00:58:56.417 --> 00:58:59.850 of these compounds and.

NOTE Confidence: 0.985358815294118

00:58:59.850 --> 00:59:03.770 What we found was that after IP

NOTE Confidence: 0.985358815294118

00:59:03.770 --> 00:59:06.325 administration they were had

NOTE Confidence: 0.985358815294118

00:59:06.325 --> 00:59:09.538 tremendous bio availability and were

NOTE Confidence: 0.985358815294118

00:59:09.538 --> 00:59:11.758 actually concentrated in the brain.

NOTE Confidence: 0.985358815294118

00:59:11.760 --> 00:59:14.128 You can see here for this compound here

NOTE Confidence: 0.985358815294118

00:59:14.130 --> 00:59:16.510 the brain to plasma ratio was about 8 to one,

NOTE Confidence: 0.985358815294118

00:59:16.510 --> 00:59:18.846 so these are extraordinarily

NOTE Confidence: 0.985358815294118

00:59:18.846 --> 00:59:21.766 good for drug like properties.

NOTE Confidence: 0.985358815294118

00:59:21.770 --> 00:59:22.148 So,

NOTE Confidence: 0.985358815294118

00:59:22.148 --> 00:59:22.526 uh.

NOTE Confidence: 0.985358815294118

00:59:22.526 --> 00:59:24.794 We decided to because there has

NOTE Confidence: 0.985358815294118

00:59:24.794 --> 00:59:27.848 been this flurry of interest that

NOTE Confidence: 0.985358815294118

00:59:27.848 --> 00:59:30.068 psychedelic drugs might have

NOTE Confidence: 0.985358815294118

00:59:30.068 --> 00:59:32.340 antidepressant drug like activity.

NOTE Confidence: 0.986049552

00:59:35.090 --> 00:59:38.605 We decided to test them in a model

NOTE Confidence: 0.986049552

00:59:38.605 --> 00:59:40.930 of antidepressive drug like activity

NOTE Confidence: 0.986049552

00:59:40.930 --> 00:59:43.722 and this this model is based on the

NOTE Confidence: 0.986049552

00:59:43.722 --> 00:59:47.000 use of beam at two heterozygote mice.

NOTE Confidence: 0.986049552

00:59:47.000 --> 00:59:49.418 So beam at two is specifically

NOTE Confidence: 0.986049552

00:59:49.418 --> 00:59:50.627 or monoamine transporter.

NOTE Confidence: 0.986049552

00:59:50.630 --> 00:59:53.248 It's the site of action of reserving

NOTE Confidence: 0.986049552

00:59:53.250 --> 00:59:55.146 psychiatrist in the audience.

NOTE Confidence: 0.986049552

00:59:55.146 --> 00:59:58.290 Will will remember that reserving was shown

NOTE Confidence: 0.986049552

00:59:58.290 --> 01:00:02.250 in the 1950s to deplete biogenic amines,

NOTE Confidence: 0.986049552

01:00:02.250 --> 01:00:05.134 which used as a as a treatment.

NOTE Confidence: 0.986049552

01:00:05.140 --> 01:00:09.132 For hypertension and as a side effect caused

NOTE Confidence: 0.986049552

01:00:09.132 --> 01:00:12.418 depression and nightmares in individuals.

NOTE Confidence: 0.986049552

01:00:12.420 --> 01:00:15.652 And so mice that that are heterozygote for

NOTE Confidence: 0.986049552

01:00:15.652 --> 01:00:19.219 beam at two have quote unquote depressive

NOTE Confidence: 0.986049552

01:00:19.220 --> 01:00:24.008 like phenotype and so so we tested

NOTE Confidence: 0.986049552

01:00:24.008 --> 01:00:26.990 these mice in the tail suspension test.

NOTE Confidence: 0.986049552

01:00:26.990 --> 01:00:30.149 You can see that the beam at hit mice

NOTE Confidence: 0.986049552

01:00:30.149 --> 01:00:32.665 have have show a longer suspension

NOTE Confidence: 0.986049552

01:00:32.665 --> 01:00:35.296 time in the tail suspension test

NOTE Confidence: 0.986049552

01:00:35.296 --> 01:00:37.636 compared to the wild type mice.

01:00:37.640 --> 01:00:40.292 20 milligrams per kilogram of luak

01:00:40.292 --> 01:00:42.410 sytin basically restores this too.

01:00:42.410 --> 01:00:46.743 Baseline and then .5 megs per kilogram

01:00:46.743 --> 01:00:50.559 and 1 milligram per kilogram of.

01:00:50.560 --> 01:00:53.227 Of of this compound in a related

01:00:53.227 --> 01:00:55.438 compound have a similar antidepressant

01:00:55.438 --> 01:00:58.180 drug like action as 20 milligrams

01:00:58.257 --> 01:01:00.000 per kilogram fluoxetine.

01:01:00.000 --> 01:01:01.925 This doesn't mean that these

01:01:01.925 --> 01:01:03.080 are antidepressant drugs,

01:01:03.080 --> 01:01:05.425 but this just that they have antidepressant

01:01:05.425 --> 01:01:08.275 drug like action in this test.

01:01:08.280 --> 01:01:09.704 Are they psychedelic now?

01:01:09.704 --> 01:01:12.881 Remember I said that we had this this

01:01:12.881 --> 01:01:14.817 intriguing evidence that arrestin

NOTE Confidence: 0.986049552

01:01:14.817 --> 01:01:18.012 signaling may have something to do with

NOTE Confidence: 0.986049552

01:01:18.012 --> 01:01:20.388 the psychedelic action of these compounds.

NOTE Confidence: 0.986049552

01:01:20.390 --> 01:01:23.064 And that these drugs tend tend not

NOTE Confidence: 0.986049552

01:01:23.064 --> 01:01:25.590 to activate the arrestin pathway,

NOTE Confidence: 0.986049552

01:01:25.590 --> 01:01:27.802 and so we tested them in the

NOTE Confidence: 0.986049552

01:01:27.802 --> 01:01:30.420 head Twitch response at.

NOTE Confidence: 0.986049552

01:01:30.420 --> 01:01:32.572 At doses that are similar to those that

NOTE Confidence: 0.986049552

01:01:32.572 --> 01:01:35.119 have an antidepressant drug like response,

NOTE Confidence: 0.986049552

01:01:35.120 --> 01:01:37.490 you can see absolutely no effect

NOTE Confidence: 0.986049552

01:01:37.490 --> 01:01:39.850 in the head Twitch response.

NOTE Confidence: 0.986049552

01:01:39.850 --> 01:01:43.570 And no effect in a locomotor response either,

NOTE Confidence: 0.986049552

01:01:43.570 --> 01:01:47.818 and and finally no effect in many many many

NOTE Confidence: 0.986049552

01:01:47.818 --> 01:01:51.569 other tests of psychedelic drug action.

NOTE Confidence: 0.986049552

01:01:51.570 --> 01:01:55.130 So what we have basically are compounds that

NOTE Confidence: 0.986049552

01:01:55.130 --> 01:01:57.826 apparently interact with five HT 2A receptor.

NOTE Confidence: 0.986049552

01:01:57.830 --> 01:01:58.718 They activate it,

NOTE Confidence: 0.986049552

01:01:58.718 --> 01:02:00.790 they have an antidepressant drug like action,

NOTE Confidence: 0.986049552

01:02:00.790 --> 01:02:03.150 but there don't have psychedelic

NOTE Confidence: 0.986049552

01:02:03.150 --> 01:02:05.926 drug like effects and so Yale has

NOTE Confidence: 0.986049552

01:02:05.926 --> 01:02:07.960 filed a patent on this compounds.

NOTE Confidence: 0.986049552

01:02:07.960 --> 01:02:08.197 Uhm,

NOTE Confidence: 0.986049552

01:02:08.197 --> 01:02:10.330 so that gives you an idea of of what

NOTE Confidence: 0.986049552

01:02:10.397 --> 01:02:12.365 we're doing and where we're going.

NOTE Confidence: 0.986049552

01:02:12.370 --> 01:02:14.414 Obviously we're very excited

NOTE Confidence: 0.986049552

01:02:14.414 --> 01:02:17.750 about these results and.

NOTE Confidence: 0.986049552

01:02:17.750 --> 01:02:20.422 Were were attempting to

NOTE Confidence: 0.986049552

01:02:20.422 --> 01:02:22.869 create even better compounds,

NOTE Confidence: 0.986049552

01:02:22.869 --> 01:02:25.503 both the psychedelic and non psychedelic

NOTE Confidence: 0.986049552

01:02:25.503 --> 01:02:28.397 that interact with the five HT 2A receptor.

NOTE Confidence: 0.986049552

01:02:28.400 --> 01:02:30.380 Ultimately to be used as chemical

NOTE Confidence: 0.986049552

01:02:30.380 --> 01:02:33.170 tools to begin to test some of the

NOTE Confidence: 0.986049552

01:02:33.170 --> 01:02:35.070 hypothesis of psychedelic drug action.

NOTE Confidence: 0.986049552

01:02:35.070 --> 01:02:38.877 It would be really important to have a

NOTE Confidence: 0.986049552

01:02:38.877 --> 01:02:43.000 drug which activates 5 HT 2A receptors.

NOTE Confidence: 0.986049552

01:02:43.000 --> 01:02:45.684 And no other receptors.

NOTE Confidence: 0.986049552

01:02:45.684 --> 01:02:49.372 If nothing else to test the hypothesis

NOTE Confidence: 0.986049552

01:02:49.372 --> 01:02:51.462 that the psychedelic effects really

NOTE Confidence: 0.986049552

01:02:51.462 --> 01:02:53.780 are due to five HT 2 receptors,

NOTE Confidence: 0.986049552

01:02:53.780 --> 01:02:54.764 and so on.

NOTE Confidence: 0.986049552

01:02:54.764 --> 01:02:57.060 And so that's that's what we're doing.

NOTE Confidence: 0.986049552

01:02:57.060 --> 01:02:58.950 As well as solving structures,

NOTE Confidence: 0.986049552

01:02:58.950 --> 01:03:01.090 I just want to thank the various folks in the

NOTE Confidence: 0.986049552

01:03:01.143 --> 01:03:03.240 in the team that that were involved in this.

NOTE Confidence: 0.986049552

01:03:03.240 --> 01:03:04.242 In this work,

NOTE Confidence: 0.986049552

01:03:04.242 --> 01:03:06.246 I think I've highlighted them all.

NOTE Confidence: 0.986049552

01:03:06.250 --> 01:03:08.390 I want to give a shout out to Bill Wetzel

NOTE Confidence: 0.962167822307692

01:03:08.443 --> 01:03:09.538 and Ramona Rodriguez.

NOTE Confidence: 0.962167822307692

01:03:09.540 --> 01:03:14.240 Denise Confair, who's now at.

NOTE Confidence: 0.962167822307692

01:03:14.240 --> 01:03:16.050 I forget which pharmaceutical company.

NOTE Confidence: 0.958506121428571

01:03:18.110 --> 01:03:21.988 Maybe AstraZeneca now from the element lab.

NOTE Confidence: 0.958506121428571

01:03:21.990 --> 01:03:23.970 Ruth Hooten Hines, Lab, Chow fan,

NOTE Confidence: 0.958506121428571

01:03:23.970 --> 01:03:26.770 Zhang Gorgo Skinny Otis lab,

NOTE Confidence: 0.958506121428571

01:03:26.770 --> 01:03:28.429 Brian Shoichet slab,

NOTE Confidence: 0.958506121428571

01:03:28.429 --> 01:03:31.610 and Dave Nichols and all the work

NOTE Confidence: 0.958506121428571

01:03:31.610 --> 01:03:33.890 is supported by your tax dollars.

NOTE Confidence: 0.958506121428571

01:03:33.890 --> 01:03:36.820 This longstanding and IMHO psychoactive

NOTE Confidence: 0.958506121428571

01:03:36.820 --> 01:03:39.164 drug screening program provides

NOTE Confidence: 0.958506121428571

01:03:39.164 --> 01:03:41.834 all the pharmacologic profiling and

NOTE Confidence: 0.958506121428571

01:03:41.834 --> 01:03:44.834 is available to anyone else who.

NOTE Confidence: 0.958506121428571

01:03:44.840 --> 01:03:46.775 Who who has interesting compounds

NOTE Confidence: 0.958506121428571

01:03:46.775 --> 01:03:49.276 they liked us to look at in

NOTE Confidence: 0.958506121428571

01:03:49.276 --> 01:03:50.738 the last three years or so,

NOTE Confidence: 0.958506121428571

01:03:50.738 --> 01:03:52.190 we've worked with more than 400

NOTE Confidence: 0.958506121428571

01:03:52.240 --> 01:03:53.790 different labs around the world,

NOTE Confidence: 0.958506121428571

01:03:53.790 --> 01:03:55.398 as well as DARPA.

NOTE Confidence: 0.958506121428571

01:03:55.398 --> 01:03:57.408 That that's funding this work,

NOTE Confidence: 0.958506121428571

01:03:57.410 --> 01:03:59.279 and I'm happy now to answer any

NOTE Confidence: 0.958506121428571

01:03:59.279 --> 01:04:00.620 questions that you may have.

NOTE Confidence: 0.958506121428571

01:04:00.620 --> 01:04:01.060 Thank you.

NOTE Confidence: 0.99135065

01:04:04.650 --> 01:04:08.249 Thank you so much. That was a comprehensive

NOTE Confidence: 0.853603372

01:04:08.250 --> 01:04:11.805 walkthrough. A lot of really

NOTE Confidence: 0.853603372

01:04:11.805 --> 01:04:14.590 impressive science, so I I am going

NOTE Confidence: 0.853603372

01:04:14.590 --> 01:04:16.612 to ask everybody who would like to

NOTE Confidence: 0.853603372

01:04:16.612 --> 01:04:18.698 ask a question live just to raise

NOTE Confidence: 0.853603372

01:04:18.698 --> 01:04:20.680 your hand using the reactions.

NOTE Confidence: 0.983654129230769

01:04:22.790 --> 01:04:25.510 Tab, because that allows me to see you

NOTE Confidence: 0.983654129230769

01:04:25.510 --> 01:04:28.622 when you ask the question and or if you'd

NOTE Confidence: 0.983654129230769

01:04:28.622 --> 01:04:30.790 rather not ask your question out loud,

NOTE Confidence: 0.983654129230769

01:04:30.790 --> 01:04:31.990 please put it in the chat.

NOTE Confidence: 0.983654129230769

01:04:31.990 --> 01:04:34.398 If there are any trainees on the line

NOTE Confidence: 0.983654129230769

01:04:34.398 --> 01:04:36.929 who would be willing to ask a question,

NOTE Confidence: 0.983654129230769

01:04:36.930 --> 01:04:39.333 that would be an ideal way to start off.

NOTE Confidence: 0.983654129230769

01:04:39.340 --> 01:04:41.980 So I'll give you one second to raise

NOTE Confidence: 0.983654129230769

01:04:41.980 --> 01:04:45.130 your hand, and if not we'll go to

NOTE Confidence: 0.983654129230769

01:04:45.130 --> 01:04:46.840 some of our more senior colleagues.

NOTE Confidence: 0.97811246

01:04:51.060 --> 01:04:54.087 OK, well in that case we'll start with

NOTE Confidence: 0.97811246

01:04:54.087 --> 01:04:56.310 Doctor Cederbaum and will let our trainees

NOTE Confidence: 0.97811246

01:04:56.310 --> 01:04:58.248 get their get their questions together.

NOTE Confidence: 0.98393462

01:05:00.720 --> 01:05:02.770 If you could unmute, yeah, thank

NOTE Confidence: 0.975308522

01:05:02.780 --> 01:05:04.180 you very much for really,

NOTE Confidence: 0.975308522

01:05:04.180 --> 01:05:06.228 really, really fascinating talk,

NOTE Confidence: 0.975308522

01:05:06.230 --> 01:05:08.690 so will disclosure here.

NOTE Confidence: 0.961635486666667

01:05:08.720 --> 01:05:10.750 I'm a neurologist and

NOTE Confidence: 0.980474487

01:05:11.000 --> 01:05:12.944 done a lot of work in the area of

NOTE Confidence: 0.980474487

01:05:12.944 --> 01:05:15.114 Parkinson's disease and one drug that's

NOTE Confidence: 0.980474487

01:05:15.114 --> 01:05:18.260 proved to be helpful in somewhat in

NOTE Confidence: 0.980474487

01:05:18.260 --> 01:05:20.880 managing delusions and hallucinations

NOTE Confidence: 0.980474487

01:05:20.880 --> 01:05:23.055 in Parkinson's disease is pimavanserin,

NOTE Confidence: 0.980474487

01:05:23.055 --> 01:05:29.032 which is a relatively selective 5 HT,

NOTE Confidence: 0.980474487

01:05:29.032 --> 01:05:31.850 25 HT 2A. Inverse agonist,

NOTE Confidence: 0.980474487

01:05:31.850 --> 01:05:33.010 as it's been characterized,

NOTE Confidence: 0.980474487

01:05:33.010 --> 01:05:34.978 and I'm wondering if you've had a chance

NOTE Confidence: 0.980474487

01:05:34.980 --> 01:05:37.610 to look at this and similar compounds,

NOTE Confidence: 0.980474487

01:05:37.610 --> 01:05:39.643 particularly with respect

NOTE Confidence: 0.980474487

01:05:39.643 --> 01:05:41.640 to how they might be

NOTE Confidence: 0.860409655

01:05:41.650 --> 01:05:48.300 biasing a receptor activity, thinking whether

NOTE Confidence: 0.988736546

01:05:48.310 --> 01:05:50.320 there is some opportunity here

NOTE Confidence: 0.988721054615385

01:05:50.330 --> 01:05:52.710 to investigate mechanisms for perhaps

NOTE Confidence: 0.988721054615385

01:05:52.710 --> 01:05:55.768 using these compounds in a preventative

NOTE Confidence: 0.988721054615385

01:05:55.768 --> 01:05:59.500 mode rather than simply a symptomatic

NOTE Confidence: 0.987517205555556

01:05:59.510 --> 01:06:00.778 treatment mode.

NOTE Confidence: 0.987517205555556

01:06:00.778 --> 01:06:05.216 Yeah, we have and we published this.

NOTE Confidence: 0.987517205555556

01:06:05.220 --> 01:06:08.400 So, uh, I'll just briefly summarize

NOTE Confidence: 0.987517205555556

01:06:08.400 --> 01:06:10.780 what we found. So one of the.

NOTE Confidence: 0.987517205555556

01:06:10.780 --> 01:06:12.688 One of the really interesting things

NOTE Confidence: 0.987517205555556

01:06:12.688 --> 01:06:15.170 about five HT 2A receptors and what.

NOTE Confidence: 0.987517205555556

01:06:15.170 --> 01:06:16.910 Basically what got me interested

NOTE Confidence: 0.987517205555556

01:06:16.910 --> 01:06:18.650 in them in the beginning.

NOTE Confidence: 0.987517205555556

01:06:18.650 --> 01:06:22.166 Uh, in the 80s? Was that, uh,

NOTE Confidence: 0.987517205555556

01:06:22.166 --> 01:06:25.396 unlike virtually all other receptors,

NOTE Confidence: 0.987517205555556

01:06:25.400 --> 01:06:28.464 antagonists cause a downregulation

NOTE Confidence: 0.987517205555556

01:06:28.464 --> 01:06:32.294 of five HT 2A receptors.

NOTE Confidence: 0.987517205555556

01:06:32.300 --> 01:06:35.724 And and it turns out it's not all

NOTE Confidence: 0.987517205555556

01:06:35.724 --> 01:06:37.729 antagonists, so some antagonists,

NOTE Confidence: 0.987517205555556

01:06:37.729 --> 01:06:39.821 downregulate 5 HT 2A

NOTE Confidence: 0.987517205555556

01:06:39.821 --> 01:06:41.565 receptors when given acutely.

NOTE Confidence: 0.987517205555556

01:06:41.565 --> 01:06:43.995 So you can give a mouse.

NOTE Confidence: 0.987517205555556

01:06:44.000 --> 01:06:46.754 A 10 milligrams per kilogram of

NOTE Confidence: 0.987517205555556

01:06:46.754 --> 01:06:49.619 clozapine and then two days later,

NOTE Confidence: 0.987517205555556

01:06:49.620 --> 01:06:51.805 five HT 2A receptors are

NOTE Confidence: 0.987517205555556

01:06:51.805 --> 01:06:54.990 downregulated 50 or 60% OK.

NOTE Confidence: 0.987517205555556

01:06:54.990 --> 01:07:01.870 Uhm, and so we wondered basically two things.

NOTE Confidence: 0.987517205555556

01:07:01.870 --> 01:07:04.257 Is this really a decrease in receptor

NOTE Confidence: 0.987517205555556

01:07:04.257 --> 01:07:06.716 number or is the is the ligand just

NOTE Confidence: 0.987517205555556

01:07:06.716 --> 01:07:08.830 trapped on the receptor that was the

NOTE Confidence: 0.987517205555556

01:07:08.830 --> 01:07:10.726 first question we wanted to answer?

NOTE Confidence: 0.987517205555556

01:07:10.730 --> 01:07:12.960 And the second one was.

NOTE Confidence: 0.987517205555556

01:07:12.960 --> 01:07:15.263 If we look at drugs that are

NOTE Confidence: 0.987517205555556

01:07:15.263 --> 01:07:17.100 therapeutic versus non therapeutic.

NOTE Confidence: 0.987517205555556

01:07:17.100 --> 01:07:19.290 Is there any segregation into

NOTE Confidence: 0.987517205555556

01:07:19.290 --> 01:07:21.480 those that cause down regulation

NOTE Confidence: 0.987517205555556

01:07:21.551 --> 01:07:23.890 versus those that don't right and

NOTE Confidence: 0.987517205555556

01:07:23.890 --> 01:07:26.500 so once so it turned out it took a

NOTE Confidence: 0.987517205555556

01:07:26.581 --> 01:07:29.179 long time to answer that question.

NOTE Confidence: 0.987517205555556

01:07:29.180 --> 01:07:30.580 And the answers were yes,

NOTE Confidence: 0.987517205555556

01:07:30.580 --> 01:07:32.757 they cause a decrease in receptor protein.

NOTE Confidence: 0.987517205555556

01:07:32.760 --> 01:07:35.490 So we definitively showed that.

NOTE Confidence: 0.987517205555556

01:07:35.490 --> 01:07:36.662 And secondly,

NOTE Confidence: 0.987517205555556

01:07:36.662 --> 01:07:39.622 there is no difference between drugs

NOTE Confidence: 0.987517205555556

01:07:39.622 --> 01:07:41.458 that are therapeutic and drugs that

NOTE Confidence: 0.987517205555556

01:07:41.458 --> 01:07:43.760 are not therapeutic in terms of whether

NOTE Confidence: 0.987517205555556

01:07:43.760 --> 01:07:45.670 they cause down regulation or not.

NOTE Confidence: 0.987517205555556

01:07:45.670 --> 01:07:47.260 So we actually looked at him

NOTE Confidence: 0.987517205555556

01:07:47.260 --> 01:07:50.500 of answer in that paper and it

NOTE Confidence: 0.987517205555556

01:07:50.500 --> 01:07:52.668 does not cause downregulation.

NOTE Confidence: 0.987517205555556

01:07:52.670 --> 01:07:55.568 Whereas clozapine ducks.

NOTE Confidence: 0.987517205555556

01:07:55.568 --> 01:07:58.466 Uhm, so uh,

NOTE Confidence: 0.987517205555556

01:07:58.470 --> 01:08:01.366 that's not to say that there isn't anything

NOTE Confidence: 0.987517205555556

01:08:01.366 --> 01:08:03.233 interesting going on, but just that.

NOTE Confidence: 0.987517205555556

01:08:03.233 --> 01:08:05.889 We're not able to see what it is yet.

NOTE Confidence: 0.987517205555556

01:08:05.890 --> 01:08:07.708 I think there might actually be

NOTE Confidence: 0.987517205555556

01:08:07.708 --> 01:08:09.110 something really interesting going on.

NOTE Confidence: 0.987517205555556

01:08:09.110 --> 01:08:12.890 We don't know what it is so.

NOTE Confidence: 0.987517205555556

01:08:12.890 --> 01:08:14.336 Great question.

NOTE Confidence: 0.987517205555556

01:08:14.336 --> 01:08:15.059 Thanks.

NOTE Confidence: 0.985065948

01:08:18.990 --> 01:08:20.380 I had a small question.

NOTE Confidence: 0.985065948

01:08:20.380 --> 01:08:22.870 It's it's some sort of about

NOTE Confidence: 0.985065948

01:08:22.870 --> 01:08:24.530 that subtle difference between

NOTE Confidence: 0.985065948

01:08:24.610 --> 01:08:26.545 the predicted docking site and

NOTE Confidence: 0.985065948

01:08:26.545 --> 01:08:28.910 then the cry OEM docking site,

NOTE Confidence: 0.985065948

01:08:28.910 --> 01:08:31.313 and I wondered if if it gave you some

NOTE Confidence: 0.985065948

01:08:31.313 --> 01:08:33.431 insight into what aspects of the in

NOTE Confidence: 0.985065948

01:08:33.431 --> 01:08:35.339 silico model needed to be tweaked,

NOTE Confidence: 0.985065948

01:08:35.340 --> 01:08:37.404 or whether it had any implications

NOTE Confidence: 0.985065948

01:08:37.404 --> 01:08:39.650 for what might change upon binding.

NOTE Confidence: 0.985539576666667

01:08:42.240 --> 01:08:44.250 We were just happy about similar

NOTE Confidence: 0.987045663333333

01:08:44.480 --> 01:08:46.930 close. Yeah, it was pretty close. It

NOTE Confidence: 0.990252546

01:08:46.940 --> 01:08:49.820 was close enough, yeah? Got

NOTE Confidence: 0.977988135

01:08:49.830 --> 01:08:51.774 it, I knew it was a small question.

NOTE Confidence: 0.984361083333333

01:08:52.090 --> 01:08:55.366 No, it's it's a great question.

NOTE Confidence: 0.984361083333333

01:08:55.370 --> 01:08:58.538 And it it turns out it.

NOTE Confidence: 0.984361083333333

01:08:58.540 --> 01:08:59.988 You know, it's technically.

NOTE Confidence: 0.986543057142857

01:09:02.660 --> 01:09:04.417 To do the experiment was like really,

NOTE Confidence: 0.986543057142857

01:09:04.420 --> 01:09:05.964 really difficult. It's technically

NOTE Confidence: 0.986543057142857

01:09:05.964 --> 01:09:08.280 a very difficult experiment to do,

NOTE Confidence: 0.986543057142857

01:09:08.280 --> 01:09:10.044 and so we were happy with that.

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NOTE Confidence: 0.986543057142857

01:09:10.050 --> 01:09:13.680 We could even see the link, and yeah.

NOTE Confidence: 0.986543057142857

01:09:13.680 --> 01:09:15.565 In in another paper that

NOTE Confidence: 0.986543057142857

01:09:15.565 --> 01:09:18.980 was published in 2019.

NOTE Confidence: 0.986543057142857

01:09:18.980 --> 01:09:21.430 In in nature, sort of,

NOTE Confidence: 0.986543057142857

01:09:21.430 --> 01:09:25.707 the first ultra large scale docking study.

NOTE Confidence: 0.986543057142857

01:09:25.710 --> 01:09:28.958 The shark at lab looked at a.

NOTE Confidence: 0.986543057142857

01:09:28.960 --> 01:09:31.636 At compounds that were were binding

NOTE Confidence: 0.986543057142857

01:09:31.636 --> 01:09:34.036 to beta lactamase so beta lactamase

NOTE Confidence: 0.986543057142857

01:09:34.036 --> 01:09:36.500 they could easily get X ray structures

NOTE Confidence: 0.986543057142857

01:09:36.565 --> 01:09:38.290 of compounds that were predicted

NOTE Confidence: 0.986543057142857

01:09:38.290 --> 01:09:40.589 to bind and were found to bind.

NOTE Confidence: 0.986543057142857

01:09:40.590 --> 01:09:43.748 And the predicted binding poses

NOTE Confidence: 0.986543057142857

01:09:43.748 --> 01:09:45.056 were actually quite good.

NOTE Confidence: 0.98796856

01:09:47.080 --> 01:09:51.750 And let me just say that.

NOTE Confidence: 0.98796856

01:09:51.750 --> 01:09:53.800 I'm not going to show it today, but.

NOTE Confidence: 0.98796856

01:09:53.800 --> 01:09:57.284 You know? I will show we have a

NOTE Confidence: 0.98796856

01:09:57.284 --> 01:09:59.139 paper in another paper in nature.

NOTE Confidence: 0.98796856

01:09:59.140 --> 01:10:00.754 That's that's impressed.

NOTE Confidence: 0.98796856

01:10:00.754 --> 01:10:03.444 Where there's another another receptor.

NOTE Confidence: 0.983901575714286

01:10:06.050 --> 01:10:07.913 Mr MRGPRX receptors,

NOTE Confidence: 0.983901575714286

01:10:07.913 --> 01:10:10.958 where we had previously predicted

NOTE Confidence: 0.983901575714286

01:10:10.958 --> 01:10:13.748 how a compound would bind.

NOTE Confidence: 0.983901575714286

01:10:13.750 --> 01:10:15.508 And when we solve this structure,

NOTE Confidence: 0.983901575714286

01:10:15.510 --> 01:10:16.538 it was completely wrong.

NOTE Confidence: 0.98977096

01:10:19.640 --> 01:10:20.868 It wasn't even close.

NOTE Confidence: 0.9920414

01:10:23.430 --> 01:10:26.210 So that's a good negative control.

NOTE Confidence: 0.9920414

01:10:26.210 --> 01:10:29.338 Yeah, doesn't always dock.

NOTE Confidence: 0.9920414

01:10:29.340 --> 01:10:30.870 Network no, that's funny.

NOTE Confidence: 0.978733775

01:10:33.250 --> 01:10:34.948 We have a question from Clara,

NOTE Confidence: 0.978733775

01:10:34.950 --> 01:10:38.358 Clara, Leo Clara. Hi, uh,

NOTE Confidence: 0.978733775

01:10:38.358 --> 01:10:40.306 first of all, thank you for that.

NOTE Confidence: 0.978733775

01:10:40.306 --> 01:10:42.908 Talk was really awesome to hear all of that.

NOTE Confidence: 0.978733775

01:10:42.910 --> 01:10:45.574 My question is in relation to

NOTE Confidence: 0.978733775

01:10:45.574 --> 01:10:47.850 the recent casarotto sell paper

NOTE Confidence: 0.978733775

01:10:47.850 --> 01:10:50.364 about Turk be binding and was

NOTE Confidence: 0.978733775

01:10:50.364 --> 01:10:53.042 wondering if you detected any Turk

NOTE Confidence: 0.978733775

01:10:53.042 --> 01:10:55.706 be activation or in your screening

NOTE Confidence: 0.978733775

01:10:55.706 --> 01:10:58.700 of binding of psychedelics.

NOTE Confidence: 0.978733775

01:10:58.700 --> 01:10:59.680 Says again.

NOTE Confidence: 0.978733775

01:10:59.680 --> 01:11:01.825 Uh, this is the casaretto cell

NOTE Confidence: 0.978733775

01:11:01.825 --> 01:11:03.928 paper that just talked about how

NOTE Confidence: 0.978733775

01:11:03.928 --> 01:11:06.250 antidepressant drug action binds to Turk.

NOTE Confidence: 0.978733775

01:11:06.250 --> 01:11:07.340 Be no

NOTE Confidence: 0.93077174

01:11:07.350 --> 01:11:10.150 track B yeah. Track fee yes yes.

NOTE Confidence: 0.875920942857143

01:11:12.850 --> 01:11:17.316 So, uh, I'm skeptical about that paper.

NOTE Confidence: 0.875920942857143

01:11:17.320 --> 01:11:21.580 Let me just say that that's all I'll say. Did

NOTE Confidence: 0.94002510125

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01:11:21.590 --> 01:11:24.454 you see any, UM, results from your screening?

NOTE Confidence: 0.97184959

01:11:25.380 --> 01:11:28.420 So we come. We don't see any signal

NOTE Confidence: 0.97184959

01:11:28.420 --> 01:11:31.079 from track fee in the proteomics.

NOTE Confidence: 0.97184959

01:11:31.080 --> 01:11:32.556 The phosphoproteomics we don't

NOTE Confidence: 0.97184959

01:11:32.556 --> 01:11:35.100 see a track B signature at all.

NOTE Confidence: 0.97184959

01:11:35.100 --> 01:11:37.620 And we don't see anything

NOTE Confidence: 0.97184959

01:11:37.620 --> 01:11:40.440 by the transcriptomics.

NOTE Confidence: 0.97184959

01:11:40.440 --> 01:11:41.946 That doesn't mean it's not involved,

NOTE Confidence: 0.97184959

01:11:41.950 --> 01:11:43.980 and I'm sure it's involved in Academy

NOTE Confidence: 0.97184959

01:11:43.980 --> 01:11:46.372 for instance, and other anti depressants.

NOTE Confidence: 0.97184959

01:11:46.372 --> 01:11:49.350 It might be that there is a.

NOTE Confidence: 0.97184959

01:11:49.350 --> 01:11:51.900 You know that psychedelic drugs?

NOTE Confidence: 0.97184959

01:11:51.900 --> 01:11:55.050 Basically have the same common endpoint,

NOTE Confidence: 0.97184959

01:11:55.050 --> 01:11:59.066 which in part is synaptogenesis, but they

NOTE Confidence: 0.97184959

01:11:59.066 --> 01:12:01.274 do it by slightly different mechanism.

NOTE Confidence: 0.97184959

01:12:01.280 --> 01:12:03.488 And if you go back to the paper

NOTE Confidence: 0.97184959

01:12:03.488 --> 01:12:06.430 that we published in 2009 uh,

NOTE Confidence: 0.97184959

01:12:06.430 --> 01:12:11.240 with Peter Pensus lab. Uhm?

NOTE Confidence: 0.97184959

01:12:11.240 --> 01:12:14.624 We we invoke basically PDZ domain

NOTE Confidence: 0.97184959

01:12:14.624 --> 01:12:17.370 proteins in in mediating the.

NOTE Confidence: 0.97184959

01:12:17.370 --> 01:12:21.720 The rapid spine formation. Uhm?

NOTE Confidence: 0.97184959

01:12:21.720 --> 01:12:25.548 Yeah so. But yeah, good question.

NOTE Confidence: 0.97184959

01:12:25.550 --> 01:12:25.820 Yeah.

NOTE Confidence: 0.916618823333333

01:12:26.740 --> 01:12:28.042 Thank you, Clara.

NOTE Confidence: 0.916618823333333

01:12:28.042 --> 01:12:30.646 Ideal do you have a question?

NOTE Confidence: 0.916618823333333

01:12:30.650 --> 01:12:35.000 Yes hi hi this is Adele Traversion time.

NOTE Confidence: 0.916618823333333

01:12:35.620 --> 01:12:37.360 From the Yale community.

NOTE Confidence: 0.916618823333333

01:12:37.360 --> 01:12:40.240 Now in clinical trials,

NOTE Confidence: 0.916618823333333

01:12:40.240 --> 01:12:44.029 UM and we do run several clinical trials,

NOTE Confidence: 0.916618823333333

01:12:44.030 --> 01:12:48.190 one in action, including psychedelics

NOTE Confidence: 0.916618823333333

01:12:48.190 --> 01:12:50.978 psilocybe in compound as,

NOTE Confidence: 0.916618823333333

01:12:50.978 --> 01:12:53.930 and so in depression.

NOTE Confidence: 0.916618823333333

01:12:53.930 --> 01:12:57.274 So, uh, this is incredibly interesting to me,

NOTE Confidence: 0.916618823333333

01:12:57.280 --> 01:13:00.097 but I have to say that I feel a

NOTE Confidence: 0.916618823333333

01:13:00.097 --> 01:13:02.143 little bit disappointed to hear

NOTE Confidence: 0.916618823333333

01:13:02.143 --> 01:13:05.440 that it's just five HT 2A receptor,

NOTE Confidence: 0.916618823333333

01:13:05.440 --> 01:13:08.876 or to try to put it together

NOTE Confidence: 0.916618823333333

01:13:08.876 --> 01:13:10.860 with what we are.

NOTE Confidence: 0.916618823333333

01:13:10.860 --> 01:13:13.318 Are experiencing or are hoping

NOTE Confidence: 0.916618823333333

01:13:13.320 --> 01:13:16.450 to see in clinic where, UM.

NOTE Confidence: 0.916618823333333

01:13:16.450 --> 01:13:23.132 Just one dose of this drug is supposedly,

NOTE Confidence: 0.916618823333333

01:13:23.132 --> 01:13:29.196 uh, going to improve or can be life changing.

NOTE Confidence: 0.916618823333333

01:13:29.196 --> 01:13:31.260 In some anecdotal things.

NOTE Confidence: 0.916618823333333

01:13:31.260 --> 01:13:34.524 For for people with depression

NOTE Confidence: 0.916618823333333

01:13:34.524 --> 01:13:36.630 or addiction etc.

NOTE Confidence: 0.916618823333333

01:13:36.630 --> 01:13:39.050 So I'm trying to put together in my mind.

NOTE Confidence: 0.916618823333333

01:13:39.050 --> 01:13:40.940 Of course we have the Academy

NOTE Confidence: 0.916618823333333

01:13:40.940 --> 01:13:42.160 in experiments as well,

NOTE Confidence: 0.916618823333333

01:13:42.160 --> 01:13:47.200 but how is it that the effect on

NOTE Confidence: 0.916618823333333

01:13:47.200 --> 01:13:52.100 5H22A account for their quite profound

NOTE Confidence: 0.916618823333333

01:13:52.100 --> 01:13:54.992 experience the patients have and we

NOTE Confidence: 0.916618823333333

01:13:54.992 --> 01:13:58.978 don't have yet the results of our trials,

NOTE Confidence: 0.916618823333333

01:13:58.980 --> 01:14:01.060 but you know,

NOTE Confidence: 0.916618823333333

01:14:01.060 --> 01:14:03.260 the initial idea that perhaps

NOTE Confidence: 0.916618823333333

01:14:03.260 --> 01:14:05.460 those are very long lasting

NOTE Confidence: 0.916618823333333

01:14:05.460 --> 01:14:10.280 changes and improvements.

NOTE Confidence: 0.916618823333333

01:14:10.280 --> 01:14:11.876 Could you speak to this little bit?

NOTE Confidence: 0.974712516538461

01:14:12.520 --> 01:14:14.816 Yeah, so first let me say that we

NOTE Confidence: 0.974712516538461

01:14:14.816 --> 01:14:17.581 don't know if it's the five HT 2A

NOTE Confidence: 0.974712516538461

01:14:17.581 --> 01:14:19.463 receptor that's responsible for the

NOTE Confidence: 0.974712516538461

01:14:19.463 --> 01:14:21.478 therapeutic action of these drugs

NOTE Confidence: 0.974712516538461

01:14:21.480 --> 01:14:24.012 because the experiments have not been

NOTE Confidence: 0.974712516538461

01:14:24.012 --> 01:14:27.940 done with five HT 2 antagonists.

NOTE Confidence: 0.974712516538461

01:14:27.940 --> 01:14:29.956 I suspect they are, but we don't know.

NOTE Confidence: 0.969564345714286

01:14:32.200 --> 01:14:36.596 The in terms of the psychedelic effects.

NOTE Confidence: 0.969564345714286

01:14:36.600 --> 01:14:39.156 Uhm, so I think we understand.

NOTE Confidence: 0.969564345714286

01:14:39.160 --> 01:14:41.472 At least I understand that maybe I can

NOTE Confidence: 0.969564345714286

01:14:41.472 --> 01:14:43.936 explain it in a way that's understandable.

NOTE Confidence: 0.969564345714286

01:14:43.940 --> 01:14:47.030 So these layer 5 pyramidal neurons

NOTE Confidence: 0.969564345714286

01:14:47.030 --> 01:14:49.420 actually serve as integrators for

NOTE Confidence: 0.969564345714286

01:14:49.420 --> 01:14:51.628 sensory and cognitive information

NOTE Confidence: 0.969564345714286

01:14:51.628 --> 01:14:53.836 throughout the entire cortex.

NOTE Confidence: 0.969564345714286

01:14:53.840 --> 01:14:56.332 So everything feeds into these into these

NOTE Confidence: 0.969564345714286

01:14:56.332 --> 01:14:59.252 layer 5 brandable neuron apical dendrites.

NOTE Confidence: 0.969564345714286

01:14:59.252 --> 01:15:02.807 They serve as basically the

NOTE Confidence: 0.969564345714286

01:15:02.807 --> 01:15:05.970 integrators for how we view reality.

NOTE Confidence: 0.969564345714286

01:15:05.970 --> 01:15:08.154 And as I as I showed you,

NOTE Confidence: 0.969564345714286

01:15:08.160 --> 01:15:11.415 what happens when LSD or some other

NOTE Confidence: 0.969564345714286

01:15:11.415 --> 01:15:14.032 drug activates these receptors is

NOTE Confidence: 0.969564345714286

01:15:14.032 --> 01:15:16.877 initially the neurons fire rapidly?

NOTE Confidence: 0.969564345714286

01:15:16.880 --> 01:15:19.334 Uh, But that's that's rather transient

NOTE Confidence: 0.969564345714286

01:15:19.334 --> 01:15:21.620 and what's sustaining to actually,

NOTE Confidence: 0.969564345714286

01:15:21.620 --> 01:15:23.640 is this increase in noise?

NOTE Confidence: 0.969564345714286

01:15:23.640 --> 01:15:26.112 So basically what we think is going on

NOTE Confidence: 0.969564345714286

01:15:26.112 --> 01:15:28.738 as you're injecting noise in the system,

NOTE Confidence: 0.969564345714286

01:15:28.740 --> 01:15:30.560 so you're basically injecting

NOTE Confidence: 0.969564345714286

01:15:30.560 --> 01:15:33.234 noise into the very neurons that

NOTE Confidence: 0.969564345714286

01:15:33.234 --> 01:15:35.598 tell you how to view reality,

NOTE Confidence: 0.969564345714286

01:15:35.600 --> 01:15:36.900 and this is then interpreted.

NOTE Confidence: 0.969564345714286

01:15:36.900 --> 01:15:37.213 Basically,

NOTE Confidence: 0.969564345714286

01:15:37.213 --> 01:15:40.595 a story is then made up by the brain for

NOTE Confidence: 0.969564345714286

01:15:40.595 --> 01:15:44.728 this or this sort of change in input.

NOTE Confidence: 0.969564345714286

01:15:44.728 --> 01:15:47.344 And we think that's the psychedelic

NOTE Confidence: 0.969564345714286

01:15:47.344 --> 01:15:50.900 experience, and it's my suspicion that.

NOTE Confidence: 0.969564345714286

01:15:50.900 --> 01:15:53.320 Uhm, and the other thing.

NOTE Confidence: 0.969564345714286

01:15:53.320 --> 01:15:55.294 The other thing that that happens

NOTE Confidence: 0.969564345714286

01:15:55.294 --> 01:15:57.454 that's I think relatively unique for

NOTE Confidence: 0.969564345714286

01:15:57.454 --> 01:15:59.409 psychedelics that we don't understand.

NOTE Confidence: 0.969564345714286

01:15:59.410 --> 01:16:03.071 Is that UM? The experience has a

NOTE Confidence: 0.969564345714286

01:16:03.071 --> 01:16:05.630 tremendous amount of salience.

NOTE Confidence: 0.969564345714286

01:16:05.630 --> 01:16:08.006 So if you talk to people that have

NOTE Confidence: 0.969564345714286

01:16:08.006 --> 01:16:09.880 taken a psychedelic drug.

NOTE Confidence: 0.969564345714286

01:16:09.880 --> 01:16:11.434 They remember it.

NOTE Confidence: 0.969564345714286

01:16:11.434 --> 01:16:15.060 It's it's a profound experience for them.

NOTE Confidence: 0.969564345714286

01:16:15.060 --> 01:16:17.335 This is not the case

NOTE Confidence: 0.969564345714286

01:16:17.335 --> 01:16:19.155 when people take ketamin.

NOTE Confidence: 0.969564345714286

01:16:19.160 --> 01:16:20.680 When they drink alcohol,

NOTE Confidence: 0.969564345714286

01:16:20.680 --> 01:16:21.820 unless they're alcoholic.

NOTE Confidence: 0.969564345714286

01:16:21.820 --> 01:16:24.452 Uh and so on.

01:16:24.452 --> 01:16:29.178 So there's something about, uh?

01:16:29.180 --> 01:16:32.414 Changing you know altering the neuronal

01:16:32.414 --> 01:16:35.060 properties of these neurons that.

01:16:35.060 --> 01:16:36.712 Uhm, in gender salience.

01:16:36.712 --> 01:16:40.399 Uh and and I don't know what that is,

01:16:40.400 --> 01:16:41.800 I I wish I did,

01:16:41.800 --> 01:16:43.718 but clearly is a five HT 2A

01:16:43.718 --> 01:16:45.360 receptor because if you block it,

01:16:45.360 --> 01:16:46.420 the drugs don't have it.

01:16:46.420 --> 01:16:48.478 They don't have a psychedelic effect.

01:16:48.480 --> 01:16:52.554 Now the the thing that we're trying

01:16:52.554 --> 01:16:54.300 to understand is.

01:16:54.300 --> 01:16:55.584 These drugs, you know,

01:16:55.584 --> 01:16:58.330 if you believe the pre click the studies.

01:16:58.330 --> 01:16:59.974 Basically a single dose

01:16:59.974 --> 01:17:01.618 is resetting the brain.

NOTE Confidence: 0.969564345714286

01:17:01.620 --> 01:17:03.540 And how is this happening?

NOTE Confidence: 0.969564345714286

01:17:03.540 --> 01:17:05.122 We don't know how it's happening and

NOTE Confidence: 0.969564345714286

01:17:05.122 --> 01:17:06.640 that's what we're trying to find out.

NOTE Confidence: 0.969564345714286

01:17:06.640 --> 01:17:11.424 So we have a huge grant from DARPA.

NOTE Confidence: 0.97914129875

01:17:14.090 --> 01:17:17.932 To to to basically do A to do a

NOTE Confidence: 0.97914129875

01:17:17.932 --> 01:17:20.740 Manhattan Project level study

NOTE Confidence: 0.97914129875

01:17:20.740 --> 01:17:23.548 of the basic biochemistry,

NOTE Confidence: 0.97914129875

01:17:23.550 --> 01:17:25.227 transcriptional machinery and

NOTE Confidence: 0.97914129875

01:17:25.227 --> 01:17:28.022 signaling downstream of five HT

NOTE Confidence: 0.97914129875

01:17:28.022 --> 01:17:30.810 2A receptors in these neurons and,

NOTE Confidence: 0.97914129875

01:17:30.810 --> 01:17:34.040 and we're hoping that will.

NOTE Confidence: 0.97914129875

01:17:34.040 --> 01:17:36.236 We'll find something out that will

NOTE Confidence: 0.97914129875

01:17:36.236 --> 01:17:38.859 begin to elucidate how these drugs work,

NOTE Confidence: 0.97914129875

01:17:38.860 --> 01:17:42.364 but I I share your frustration as well.

NOTE Confidence: 0.97914129875

01:17:42.370 --> 01:17:45.910 Sadly, there isn't a lot of

114

NOTE Confidence: 0.97914129875

01:17:45.910 --> 01:17:47.070 funded research on psychedelics,

NOTE Confidence: 0.97914129875

01:17:47.070 --> 01:17:50.112 so I think right now I have the only

NOTE Confidence: 0.97914129875

01:17:50.120 --> 01:17:53.648 NIH funded grant to study the basic

NOTE Confidence: 0.97914129875

01:17:53.648 --> 01:17:56.299 science of psychedelic drug action.

NOTE Confidence: 0.97914129875

01:17:56.300 --> 01:17:57.968 So until until we have more

NOTE Confidence: 0.97914129875

01:17:57.968 --> 01:17:59.390 investigators in the field work,

NOTE Confidence: 0.97914129875

01:17:59.390 --> 01:17:59.978 we're going to,

NOTE Confidence: 0.97914129875

01:17:59.978 --> 01:18:01.350 we're going to have a lot of

NOTE Confidence: 0.97914129875

01:18:01.396 --> 01:18:04.132 these unknowns and and I share

NOTE Confidence: 0.97914129875

01:18:04.132 --> 01:18:06.475 your frustrations as well.

NOTE Confidence: 0.97914129875

01:18:06.475 --> 01:18:09.500 Write, write to your congressman

NOTE Confidence: 0.97914129875

01:18:09.500 --> 01:18:11.130 and the Institute of Directors.

NOTE Confidence: 0.97771771

01:18:13.510 --> 01:18:17.000 I see Gerard Merrick yeah Gerard

NOTE Confidence: 0.962264735625

01:18:17.270 --> 01:18:20.240 before we high Gerard go ahead hello get to

NOTE Confidence: 0.962264735625

01:18:20.240 --> 01:18:23.730 a couple of questions from the chat. Great

NOTE Confidence: 0.929525422

01:18:23.740 --> 01:18:24.936 talk as usual Brian.

NOTE Confidence: 0.929525422

01:18:24.936 --> 01:18:27.114 I always enjoy your talks but one of

NOTE Confidence: 0.929525422

01:18:27.114 --> 01:18:28.905 the questions I was curious about.

NOTE Confidence: 0.929525422

01:18:28.905 --> 01:18:30.930 You know obviously speaking about

NOTE Confidence: 0.929525422

01:18:30.930 --> 01:18:32.812 the salience of what hallucinogens

NOTE Confidence: 0.929525422

01:18:32.812 --> 01:18:34.828 are doing and like the ideal

NOTE Confidence: 0.929525422

01:18:34.828 --> 01:18:36.718 one dose effects when you start

NOTE Confidence: 0.982586836

01:18:36.730 --> 01:18:38.940 moving though to the compounds that

NOTE Confidence: 0.987253764444444

01:18:39.210 --> 01:18:41.290 are not affecting the head

NOTE Confidence: 0.987253764444444

01:18:41.290 --> 01:18:42.954 Twitch response for example.

NOTE Confidence: 0.987253764444444

01:18:42.960 --> 01:18:44.560 What are you sort of imagining?

NOTE Confidence: 0.987253764444444

01:18:44.560 --> 01:18:45.250 'cause I was sort of

NOTE Confidence: 0.98024081

01:18:45.260 --> 01:18:46.380 thinking to what degree

NOTE Confidence: 0.9850161475

01:18:46.390 --> 01:18:47.290 do you think that

NOTE Confidence: 0.985444105

01:18:47.630 --> 01:18:49.580 there may be some similarities

NOTE Confidence: 0.985444105

01:18:49.580 --> 01:18:52.100 between just simply blockade

NOTE Confidence: 0.985444105

01:18:52.100 --> 01:18:55.190 of two a receptors versus the

NOTE Confidence: 0.985444105

01:18:55.190 --> 01:18:57.388 downregulation of two a receptors

NOTE Confidence: 0.985444105

01:18:57.388 --> 01:18:59.680 that are occurring with lucid gems?

NOTE Confidence: 0.985444105

01:18:59.680 --> 01:19:01.360 And to what extent are those?

NOTE Confidence: 0.985444105

01:19:01.360 --> 01:19:03.045 I guess it's empirical question

NOTE Confidence: 0.985444105

01:19:03.045 --> 01:19:05.670 to what extent different pathways

NOTE Confidence: 0.980896062

01:19:04.510 --> 01:19:05.610 going to be down right? But

NOTE Confidence: 0.989997537142857

01:19:05.670 --> 01:19:08.145 what are your initial thoughts

NOTE Confidence: 0.989997537142857

01:19:08.145 --> 01:19:09.770 right now? I don't know.

NOTE Confidence: 0.982967608333333

01:19:12.720 --> 01:19:17.099 I I wish I had something. Smart to say.

NOTE Confidence: 0.984674394166667

01:19:19.090 --> 01:19:20.434 I love that answer. That's the

NOTE Confidence: 0.984674394166667

01:19:20.434 --> 01:19:21.719 best answer I've ever tried to

NOTE Confidence: 0.98767509125

01:19:21.730 --> 01:19:24.330 find out what the hell is going on.

NOTE Confidence: 0.98767509125

01:19:24.330 --> 01:19:26.070 It's pretty mysterious to me too,

NOTE Confidence: 0.98767509125

01:19:26.070 --> 01:19:28.962 so I'll keep following you.

NOTE Confidence: 0.98767509125

01:19:28.962 --> 01:19:30.000 Certainly yeah, yeah,

NOTE Confidence: 0.980230150666667

01:19:30.860 --> 01:19:33.132 let me ask a couple of questions from

NOTE Confidence: 0.980230150666667

01:19:33.132 --> 01:19:35.303 the from the chat so Christian Maury

NOTE Confidence: 0.980230150666667

01:19:35.303 --> 01:19:37.654 asks do you think that the longevity

NOTE Confidence: 0.980230150666667

01:19:37.654 --> 01:19:40.244 of LSD action in the receptor also

NOTE Confidence: 0.980230150666667

01:19:40.244 --> 01:19:42.400 contributes to the rapidity of development

NOTE Confidence: 0.980230150666667

01:19:42.400 --> 01:19:44.649 of tolerance reported by users of LSD?

NOTE Confidence: 0.98705044625

01:19:44.960 --> 01:19:47.584 Yeah yeah. So what I think it does.

NOTE Confidence: 0.98705044625

01:19:47.590 --> 01:19:51.008 So what? One of the things that LSD

NOTE Confidence: 0.98705044625

01:19:51.008 --> 01:19:53.436 does is it also down regulates 5 HT

NOTE Confidence: 0.98705044625

01:19:53.436 --> 01:19:55.392 2A receptors with a single dose,

NOTE Confidence: 0.98705044625

01:19:55.400 --> 01:19:58.070 and it's likely that that long

NOTE Confidence: 0.98705044625

01:19:58.070 --> 01:20:00.154 residence time in the receptor

NOTE Confidence: 0.98705044625

01:20:00.154 --> 01:20:02.954 contributes to that and that that is

NOTE Confidence: 0.98705044625

01:20:02.954 --> 01:20:04.959 likely why there there's tolerance

NOTE Confidence: 0.98705044625

01:20:04.960 --> 01:20:09.980 that people see so anecdotally.

NOTE Confidence: 0.98705044625

01:20:09.980 --> 01:20:12.554 Nope. Four to seven days after

NOTE Confidence: 0.98705044625

01:20:12.554 --> 01:20:14.970 a dose is required before.

NOTE Confidence: 0.985328286

01:20:16.980 --> 01:20:18.890 Psychedelics have an effect so.

NOTE Confidence: 0.980663148518519

01:20:21.130 --> 01:20:23.202 So I have a question about the

NOTE Confidence: 0.980663148518519

01:20:23.202 --> 01:20:25.194 beautiful graph with all of the

NOTE Confidence: 0.980663148518519

01:20:25.194 --> 01:20:26.586 metabotropic receptors on the

NOTE Confidence: 0.980663148518519

01:20:26.586 --> 01:20:28.100 right and different psychedelic

NOTE Confidence: 0.980663148518519

01:20:28.100 --> 01:20:30.536 compounds along the top from Marilee.

NOTE Confidence: 0.980663148518519

01:20:30.540 --> 01:20:33.728 Thomas says that it looks like

NOTE Confidence: 0.980663148518519

01:20:33.728 --> 01:20:35.840 M2M3 and M4 had no psychedelic

NOTE Confidence: 0.980663148518519

01:20:35.921 --> 01:20:38.006 activity and is that correct?

NOTE Confidence: 0.980663148518519

01:20:38.010 --> 01:20:40.514 Yes, she says she's surprised 'cause

NOTE Confidence: 0.980663148518519

01:20:40.514 --> 01:20:41.918 she thought muscarinic receptors

NOTE Confidence: 0.980663148518519

01:20:41.918 --> 01:20:43.798 were all activated by muscarine and

NOTE Confidence: 0.980663148518519

01:20:43.798 --> 01:20:45.092 it has hallucinogenics properties.

NOTE Confidence: 0.980663148518519

119

01:20:45.092 --> 01:20:47.288 And can you comment on that?

NOTE Confidence: 0.980663148518519

01:20:47.530 --> 01:20:50.420 Yeah so.

NOTE Confidence: 0.989514926

01:20:50.420 --> 01:20:53.120 Their hallucinogenic, but not psychedelic.

NOTE Confidence: 0.989514926

01:20:53.120 --> 01:20:54.720 So there is there.

NOTE Confidence: 0.989514926

01:20:54.720 --> 01:20:55.920 Is this distinction.

NOTE Confidence: 0.989514926

01:20:55.920 --> 01:20:58.300 We we in the field, make between a drug,

NOTE Confidence: 0.989514926

01:20:58.300 --> 01:20:59.640 that psychedelic and drug,

NOTE Confidence: 0.989514926

01:20:59.640 --> 01:21:01.336 that solution, new genics.

NOTE Confidence: 0.989514926

01:21:01.336 --> 01:21:03.456 So many drugs are hallucinogenic.

NOTE Confidence: 0.989514926

01:21:03.460 --> 01:21:06.856 As I said, Salvador and Ibogaine.

NOTE Confidence: 0.989514926

01:21:06.860 --> 01:21:08.009 Scope, alameen etc.

NOTE Confidence: 0.989514926

01:21:08.009 --> 01:21:10.307 And then there are drugs that

NOTE Confidence: 0.989514926

01:21:10.307 --> 01:21:12.800 are psychedelic and psychedelic.

NOTE Confidence: 0.989514926

01:21:12.800 --> 01:21:16.146 Drugs are five HT two agonist so.

NOTE Confidence: 0.989514926

01:21:16.150 --> 01:21:17.050 But good question.

NOTE Confidence: 0.971053532352941

01:21:18.520 --> 01:21:20.900 And then a question about signaling and

NOTE Confidence: 0.971053532352941

01:21:20.900 --> 01:21:23.645 and it sounds like different ligands

NOTE Confidence: 0.971053532352941

01:21:23.645 --> 01:21:25.849 induce different signaling responses.

NOTE Confidence: 0.971053532352941

01:21:25.850 --> 01:21:28.550 How do naturally occurring agonists

NOTE Confidence: 0.971053532352941

01:21:28.550 --> 01:21:31.390 compare, e.g LSD versus masculine?

NOTE Confidence: 0.791706

01:21:33.900 --> 01:21:37.510 Ah. There are differences.

NOTE Confidence: 0.946161291333333

01:21:39.580 --> 01:21:42.702 And, uh. We're putting together a big

NOTE Confidence: 0.946161291333333

01:21:42.702 --> 01:21:46.080 paper where we're looking at all of these.

NOTE Confidence: 0.946161291333333

01:21:46.080 --> 01:21:48.272 All I can say is every compound is

NOTE Confidence: 0.946161291333333

01:21:48.272 --> 01:21:51.920 sort of unique and it depends on how.

NOTE Confidence: 0.946161291333333

01:21:51.920 --> 01:21:55.358 Uhm, at what level you look at it so,

NOTE Confidence: 0.946161291333333

01:21:55.360 --> 01:21:57.592 but it's I would say it's not clear

NOTE Confidence: 0.946161291333333

01:21:57.592 --> 01:21:59.803 yet that we're able to pick anything

NOTE Confidence: 0.946161291333333

01:21:59.803 --> 01:22:01.750 up that separates psychedelic

NOTE Confidence: 0.946161291333333

01:22:01.750 --> 01:22:05.250 for non psychedelic 2 agonist. So

NOTE Confidence: 0.938735652941176

01:22:05.260 --> 01:22:07.115 that question was from Zoran

NOTE Confidence: 0.938735652941176

01:22:07.115 --> 01:22:09.375 Similou who also says that five

NOTE Confidence: 0.938735652941176

01:22:09.375 --> 01:22:11.397 HT 2A is also an autoreceptor.

NOTE Confidence: 0.938735652941176

01:22:11.400 --> 01:22:12.984 In some serotonin synapses,

NOTE Confidence: 0.938735652941176

01:22:12.984 --> 01:22:15.360 and one proposal has been that

NOTE Confidence: 0.938735652941176

01:22:15.438 --> 01:22:17.682 blocking the autoreceptors might

NOTE Confidence: 0.938735652941176

01:22:17.682 --> 01:22:19.926 enhance serotonin transmission and

NOTE Confidence: 0.938735652941176

01:22:19.926 --> 01:22:22.760 therefore help antidepressant response.

NOTE Confidence: 0.938735652941176

01:22:22.760 --> 01:22:25.091 So can you sort of speculate about

NOTE Confidence: 0.938735652941176

01:22:25.091 --> 01:22:27.163 how LSD and other experimental

NOTE Confidence: 0.938735652941176

01:22:27.163 --> 01:22:29.648 agonists would fit into that?

NOTE Confidence: 0.938735652941176

01:22:29.650 --> 01:22:31.516 That aspect of the theoretical picture,

NOTE Confidence: 0.938735652941176

01:22:31.520 --> 01:22:32.788 especially in terms of?

NOTE Confidence: 0.989053522

01:22:35.320 --> 01:22:40.496 I'm not aware. Of any. Data.

NOTE Confidence: 0.989053522

01:22:40.496 --> 01:22:43.424 Any reliable data that the five HT 2A

NOTE Confidence: 0.989053522

01:22:43.424 --> 01:22:45.739 receptor is an inhibitory autoreceptor

NOTE Confidence: 0.989053522

01:22:45.739 --> 01:22:48.084 at any synapse its excitatory.

NOTE Confidence: 0.23728979

01:22:50.220 --> 01:22:55.950 Uh. And we actually only find it.

NOTE Confidence: 0.23728979

01:22:55.950 --> 01:22:58.302 So we we published a large number

NOTE Confidence: 0.23728979

01:22:58.302 --> 01:23:00.881 of papers on the localization of

NOTE Confidence: 0.23728979

01:23:00.881 --> 01:23:03.726 five HT 2A receptors by EM. In fact,

NOTE Confidence: 0.23728979

01:23:03.726 --> 01:23:06.016 we've never found it presynaptically.

NOTE Confidence: 0.23728979

01:23:06.020 --> 01:23:08.150 It's always been post synaptically so.

NOTE Confidence: 0.9832971625

01:23:11.600 --> 01:23:13.288 So I I don't know about that data,

NOTE Confidence: 0.9832971625

01:23:13.290 --> 01:23:14.616 so I can't comment on it.

NOTE Confidence: 0.99192685

01:23:16.680 --> 01:23:20.780 Great, so I think it's 11:40,

NOTE Confidence: 0.989319653333333

01:23:20.780 --> 01:23:24.102 so we should. Maybe stop it there.

NOTE Confidence: 0.989319653333333

01:23:24.102 --> 01:23:25.680 It has been a pleasure to

NOTE Confidence: 0.989319653333333

01:23:25.739 --> 01:23:27.169 spend this time with you.

NOTE Confidence: 0.989319653333333

01:23:27.170 --> 01:23:29.170 I just wanted to let you know that

NOTE Confidence: 0.989319653333333

01:23:29.170 --> 01:23:30.486 Doctor Agajanian was able to join

NOTE Confidence: 0.989319653333333

01:23:30.486 --> 01:23:32.782 us for part of the great great and

NOTE Confidence: 0.989319653333333

01:23:32.782 --> 01:23:34.835 I I I can send you his email if you

NOTE Confidence: 0.989319653333333

01:23:34.835 --> 01:23:36.704 want to reach out to him afterward.

NOTE Confidence: 0.989319653333333

01:23:36.710 --> 01:23:38.622 I want to thank everybody for your great

NOTE Confidence: 0.989319653333333

01:23:38.622 --> 01:23:40.207 questions and for being with us today.

NOTE Confidence: 0.989319653333333

01:23:40.210 --> 01:23:42.338 So thank you Brian.

NOTE Confidence: 0.96721886375

01:23:42.410 --> 01:23:45.170 Oh, and can you send me a link

NOTE Confidence: 0.96721886375

01:23:45.170 --> 01:23:47.114 so that I can meet with the with

NOTE Confidence: 0.96721886375

01:23:47.114 --> 01:23:48.680 the students and everybody else?

NOTE Confidence: 0.96721886375

01:23:48.680 --> 01:23:50.252 Absolutely I'll do that right now.

NOTE Confidence: 0.96721886375

01:23:50.252 --> 01:23:53.000 Thank you. Bye bye.