WEBVTT

00:00:03.370 --> 00:00:05.841 Marina, thank you so much for that

00:00:05.841 --> 00:00:07.648 really great introduction and I'm let

00:00:07.648 --> 00:00:09.610 me share my screen and I do that.

00:00:09.610 --> 00:00:13.508 You know, it's it's quite an honor to

00:00:13.508 --> 00:00:17.834 be given this opportunity to be the.

00:00:17.840 --> 00:00:20.759 Ribicoff speaker for for this year and

00:00:20.759 --> 00:00:23.790 especially that great list of of previous

00:00:23.790 --> 00:00:26.636 speakers and just for me, I think.

00:00:26.636 --> 00:00:27.620 And obviously everybody.

00:00:27.620 --> 00:00:30.385 I think Yale has a great reputation

00:00:30.385 --> 00:00:32.464 of understanding the importance of

00:00:32.464 --> 00:00:34.918 evidence based medicine and the only

00:00:34.918 --> 00:00:37.578 way for us to really get there and

00:00:37.578 --> 00:00:39.414 move the field forward is having

NOTE Confidence: 0.847070010952381

00:00:39.414 --> 00:00:41.388 this close interaction between basic

NOTE Confidence: 0.847070010952381

00:00:41.388 --> 00:00:43.398 scientists and clinical and the

NOTE Confidence: 0.847070010952381

00:00:43.398 --> 00:00:45.540 and the clinical and clinicians.

NOTE Confidence: 0.847070010952381

00:00:45.540 --> 00:00:48.666 So again, thanks for this opportunity.

NOTE Confidence: 0.847070010952381

00:00:48.670 --> 00:00:52.598 So I'm going to move all the lovely

NOTE Confidence: 0.847070010952381

00:00:52.598 --> 00:00:54.775 pictures of everyone and the first

NOTE Confidence: 0.847070010952381

00:00:54.775 --> 00:00:57.639 thing I will say is that you know

NOTE Confidence: 0.847070010952381

00:00:57.639 --> 00:00:59.841 I don't have anything to dispose

NOTE Confidence: 0.847070010952381

00:00:59.841 --> 00:01:02.646 in terms of the the work that I'll

NOTE Confidence: 0.847070010952381

00:01:02.646 --> 00:01:04.881 be talking to you about today.

NOTE Confidence: 0.847070010952381

00:01:04.881 --> 00:01:07.323 And basically you know for me,

NOTE Confidence: 0.847070010952381

00:01:07.330 --> 00:01:09.460 the Addiction Institute of Mount

NOTE Confidence: 0.847070010952381

00:01:09.460 --> 00:01:12.858 Sinai that I direct is.

NOTE Confidence: 0.847070010952381

00:01:12.860 --> 00:01:15.422 It brought home the critical nature of

NOTE Confidence: 0.847070010952381

00:01:15.422 --> 00:01:18.176 of research and where we are today,

NOTE Confidence: 0.847070010952381

00:01:18.180 --> 00:01:20.595 and the reason is in large part

NOTE Confidence: 0.847070010952381

00:01:20.595 --> 00:01:23.188 when we think about a lot of the

NOTE Confidence: 0.847070010952381

00:01:23.188 --> 00:01:24.820 substance use disorders at Mount Sinai,

NOTE Confidence: 0.847070010952381

00:01:24.820 --> 00:01:26.560 we treat over 6000 people with

NOTE Confidence: 0.847070010952381

00:01:26.560 --> 00:01:27.720 an opiate use disorder.

NOTE Confidence: 0.847070010952381

00:01:27.720 --> 00:01:29.953 So you can imagine the the challenges

NOTE Confidence: 0.847070010952381

00:01:29.953 --> 00:01:32.035 there and it really reflects the

NOTE Confidence: 0.847070010952381

00:01:32.035 --> 00:01:34.492 opioid crisis that we are still in.

NOTE Confidence: 0.847070010952381

00:01:34.500 --> 00:01:35.748 And as many of you know,

NOTE Confidence: 0.847070010952381

00:01:35.750 --> 00:01:37.925 you know the economic burden

NOTE Confidence: 0.847070010952381

00:01:37.925 --> 00:01:39.845 of the opioid crisis.

NOTE Confidence: 0.847070010952381

00:01:39.845 --> 00:01:41.825 The healthcare system under

NOTE Confidence: 0.847070010952381

00:01:41.825 --> 00:01:43.310 siege because it's.

NOTE Confidence: 0.847070010952381

00:01:43.310 --> 00:01:44.510 It does cost a lot,

NOTE Confidence: 0.847070010952381

00:01:44.510 --> 00:01:46.827 is it's costing nearly three times more

NOTE Confidence: 0.847070010952381

3

00:01:46.827 --> 00:01:48.970 than other medical disorders to trade,

NOTE Confidence: 0.847070010952381

00:01:48.970 --> 00:01:50.752 and the treatments that are that

NOTE Confidence: 0.847070010952381

00:01:50.752 --> 00:01:52.469 are available are often not used,

NOTE Confidence: 0.847070010952381

00:01:52.470 --> 00:01:55.868 and some of them not suitable and we

NOTE Confidence: 0.847070010952381

00:01:55.868 --> 00:01:58.622 still have so many overdose deaths

NOTE Confidence: 0.847070010952381

00:01:58.622 --> 00:02:01.901 today and that has been the crisis

NOTE Confidence: 0.847070010952381

00:02:01.901 --> 00:02:04.486 have been exacerbated by covid's.

NOTE Confidence: 0.847070010952381

00:02:04.490 --> 00:02:06.530 COVID has exacerbated so many things,

NOTE Confidence: 0.847070010952381

00:02:06.530 --> 00:02:08.594 but the stress and social isolation

NOTE Confidence: 0.847070010952381

00:02:08.594 --> 00:02:09.970 has increased drug use.

NOTE Confidence: 0.847070010952381

00:02:09.970 --> 00:02:10.660 And of course,

NOTE Confidence: 0.847070010952381

00:02:10.660 --> 00:02:12.270 you see that a lot with opioids,

NOTE Confidence: 0.847070010952381

00:02:12.270 --> 00:02:14.160 and especially unfortunately.

NOTE Confidence: 0.847070010952381

00:02:14.160 --> 00:02:15.420 With fentanyl,

NOTE Confidence: 0.847070010952381

00:02:15.420 --> 00:02:18.624 that 4th wave of opioids that

NOTE Confidence: 0.847070010952381

00:02:18.624 --> 00:02:21.300 contribute significantly to to dread

00:02:21.300 --> 00:02:23.900 to drug overdose and so that you know.

00:02:23.900 --> 00:02:26.618 During COVID you've seen so many

00:02:26.618 --> 00:02:29.240 more people dying of opioid overdose,

00:02:29.240 --> 00:02:30.500 so you know.

00:02:30.500 --> 00:02:33.020 So for me, the question has always been,

00:02:33.020 --> 00:02:35.180 you know, how can we improve?

00:02:35.180 --> 00:02:37.007 What's what we're doing and a part

00:02:37.007 --> 00:02:38.878 of that comes back to treatments.

00:02:38.880 --> 00:02:40.668 And when you look at treatments

00:02:40.668 --> 00:02:41.860 for substance use disorders,

00:02:41.860 --> 00:02:44.348 you know there is actually a long history.

00:02:44.350 --> 00:02:47.008 And it's interesting that there were

00:02:47.008 --> 00:02:49.275 morphine maintenance clinics already in 1919,

00:02:49.275 --> 00:02:52.020 and as you look across the years of the

00:02:52.096 --> 00:02:54.606 medications that have been developed.

00:02:54.610 --> 00:02:55.702 There've been a number.

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00:02:55.702 --> 00:02:57.722 I'm going to focus on the opioids

NOTE Confidence: 0.847070010952381

00:02:57.722 --> 00:02:59.630 because most of the the treatments

NOTE Confidence: 0.847070010952381

00:02:59.630 --> 00:03:01.608 that have been developed and hear

NOTE Confidence: 0.847070010952381

00:03:01.608 --> 00:03:04.530 from 1964 with methadone to today.

NOTE Confidence: 0.847070010952381

00:03:04.530 --> 00:03:07.946 They are all focused on the opioid system.

NOTE Confidence: 0.847070010952381

00:03:07.950 --> 00:03:11.286 So opioid agonist in large part,

NOTE Confidence: 0.847070010952381

00:03:11.290 --> 00:03:12.978 not only methadone, buprenorphine,

NOTE Confidence: 0.847070010952381

00:03:12.978 --> 00:03:14.244 and of course,

NOTE Confidence: 0.883464144

00:03:14.250 --> 00:03:16.410 we have naltrexone,

NOTE Confidence: 0.883464144

00:03:16.410 --> 00:03:19.998 especially for trying to reduce overdose.

NOTE Confidence: 0.883464144

00:03:19.998 --> 00:03:22.342 And there are, of course

NOTE Confidence: 0.883464144

00:03:22.342 --> 00:03:23.806 behavioral therapies as well,

NOTE Confidence: 0.883464144

00:03:23.810 --> 00:03:25.680 but as I mentioned earlier,

NOTE Confidence: 0.883464144

00:03:25.680 --> 00:03:27.432 the problem that we have with a lot

NOTE Confidence: 0.883464144

00:03:27.432 --> 00:03:29.361 of the treatments is that only about

NOTE Confidence: 0.883464144

00:03:29.361 --> 00:03:31.540 20% of the people who need opioid

NOTE Confidence: 0.883464144

00:03:31.540 --> 00:03:33.020 use treatment actually receive it,

NOTE Confidence: 0.883464144

00:03:33.020 --> 00:03:35.420 and the the reasons are numerous

NOTE Confidence: 0.883464144

00:03:35.420 --> 00:03:37.899 things start with even the stigma,

NOTE Confidence: 0.883464144

00:03:37.900 --> 00:03:38.686 because unfortunately,

NOTE Confidence: 0.883464144

00:03:38.686 --> 00:03:41.044 even though these medications do work,

NOTE Confidence: 0.883464144

00:03:41.050 --> 00:03:43.160 they've saved millions of lives.

NOTE Confidence: 0.883464144

00:03:43.160 --> 00:03:46.640 The stigma associated with with opioid

NOTE Confidence: 0.883464144

00:03:46.640 --> 00:03:49.214 agonist and many programs not wanting

NOTE Confidence: 0.883464144

00:03:49.214 --> 00:03:52.123 to quote UN quote their their their

NOTE Confidence: 0.883464144

00:03:52.123 --> 00:03:54.384 clients to be on any medication.

NOTE Confidence: 0.883464144

00:03:54.384 --> 00:03:56.808 That might be have an addictive

NOTE Confidence: 0.883464144

00:03:56.808 --> 00:03:57.616 potential itself,

NOTE Confidence: 0.883464144

00:03:57.620 --> 00:03:59.538 so there are these challenges as well.

NOTE Confidence: 0.883464144

00:03:59.540 --> 00:04:00.820 And ironically,

NOTE Confidence: 0.883464144

00:04:00.820 --> 00:04:02.740 the governmental regulations

NOTE Confidence: 0.883464144

00:04:02.740 --> 00:04:05.300 of using these opioid.

NOTE Confidence: 0.883464144

00:04:05.300 --> 00:04:07.540 Treatments make it very challenging,

NOTE Confidence: 0.883464144

00:04:07.540 --> 00:04:09.225 clinically and for patients to

NOTE Confidence: 0.883464144

00:04:09.225 --> 00:04:10.573 even access these treatments,

NOTE Confidence: 0.883464144

00:04:10.580 --> 00:04:12.548 sometimes in places in the US

NOTE Confidence: 0.883464144

00:04:12.548 --> 00:04:14.674 where people have to drive or find

NOTE Confidence: 0.883464144

00:04:14.674 --> 00:04:16.880 a way to get to them for hours.

NOTE Confidence: 0.883464144

00:04:16.880 --> 00:04:20.273 And as I said, from 19 six to four,

NOTE Confidence: 0.883464144

00:04:20.280 --> 00:04:22.856 we really have had this one size fit

NOTE Confidence: 0.883464144

00:04:22.856 --> 00:04:25.678 all approach to treating opiate use disorder.

NOTE Confidence: 0.883464144

00:04:25.680 --> 00:04:27.731 So for me, when you look at

NOTE Confidence: 0.883464144

00:04:27.731 --> 00:04:29.300 the neurobiology of addiction,

NOTE Confidence: 0.883464144

00:04:29.300 --> 00:04:31.004 you know the question is what

NOTE Confidence: 0.883464144

00:04:31.004 --> 00:04:31.856 have we learned?

NOTE Confidence: 0.883464144

00:04:31.860 --> 00:04:34.100 We have learned a lot really a lot.

NOTE Confidence: 0.883464144

00:04:34.100 --> 00:04:35.570 We have learned a lot about.

NOTE Confidence: 0.883464144

00:04:35.570 --> 00:04:37.778 Different brain regions and

NOTE Confidence: 0.883464144

00:04:37.778 --> 00:04:39.986 neural circuits relevant to

NOTE Confidence: 0.883464144

00:04:39.990 --> 00:04:42.002 phenotypes important for addiction.

NOTE Confidence: 0.883464144

00:04:42.002 --> 00:04:43.008 For example,

NOTE Confidence: 0.883464144

00:04:43.010 --> 00:04:45.117 the ventral steroidal area that which is

NOTE Confidence: 0.883464144

00:04:45.117 --> 00:04:47.128 a nucleus accumbens important for reward,

NOTE Confidence: 0.883464144

00:04:47.130 --> 00:04:49.426 expectation, goal directed behavior.

NOTE Confidence: 0.883464144

00:04:49.426 --> 00:04:51.148 The dorsal striatum.

NOTE Confidence: 0.883464144

00:04:51.150 --> 00:04:54.130 Important for habit, habitual formation,

NOTE Confidence: 0.883464144

00:04:54.130 --> 00:04:55.180 the prefrontal cortex,

NOTE Confidence: 0.883464144

00:04:55.180 --> 00:04:57.923 and the number of the it's sub regions

NOTE Confidence: 0.883464144

00:04:57.923 --> 00:05:00.426 such as the orbital frontal region.

NOTE Confidence: 0.883464144

00:05:00.426 --> 00:05:04.000 Cognitive control goal, directed behavior.

NOTE Confidence: 0.883464144

00:05:04.000 --> 00:05:05.810 Cognitive flexibility.

NOTE Confidence: 0.883464144

00:05:05.810 --> 00:05:08.130 Emotional regulation and so on.

NOTE Confidence: 0.883464144

00:05:08.130 --> 00:05:10.934 And we do know that for the most

NOTE Confidence: 0.883464144

00:05:10.934 --> 00:05:13.090 drugs of abuse that the use acute

NOTE Confidence: 0.883464144

00:05:13.158 --> 00:05:15.097 use of the drug does lead to,

NOTE Confidence: 0.883464144

00:05:15.100 --> 00:05:15.998 for example,

NOTE Confidence: 0.883464144

00:05:15.998 --> 00:05:17.794 this increasing dopamine that's

NOTE Confidence: 0.883464144

00:05:17.794 --> 00:05:21.210 associated with business phoria and

NOTE Confidence: 0.883464144

00:05:21.210 --> 00:05:24.066 so many research has gone into this.

NOTE Confidence: 0.883464144

00:05:24.070 --> 00:05:27.830 This acute changes that occurs with drug use.

NOTE Confidence: 0.883464144

00:05:27.830 --> 00:05:28.619 So for me,

NOTE Confidence: 0.883464144

00:05:28.619 --> 00:05:30.460 a quick question that I asked many

NOTE Confidence: 0.883464144

00:05:30.519 --> 00:05:32.682 many years ago that then became the

NOTE Confidence: 0.883464144

00:05:32.682 --> 00:05:34.657 foundation for my research was really

NOTE Confidence: 0.883464144

00:05:34.657 --> 00:05:37.322 what have we learned about the human brain,

NOTE Confidence: 0.883464144

00:05:37.322 --> 00:05:38.810 especially the molecular level.

NOTE Confidence: 0.883464144

00:05:38.810 --> 00:05:40.675 Because it was so challenging

NOTE Confidence: 0.883464144

00:05:40.675 --> 00:05:43.310 to get that kind of insights.

NOTE Confidence: 0.883464144

00:05:43.310 --> 00:05:44.750 And so I thought,

NOTE Confidence: 0.883464144

00:05:44.750 --> 00:05:45.110 OK,

NOTE Confidence: 0.883464144

00:05:45.110 --> 00:05:46.678 let's start studying the

NOTE Confidence: 0.883464144

00:05:46.678 --> 00:05:47.854 postmortem human brain.

NOTE Confidence: 0.883464144

00:05:47.860 --> 00:05:51.227 And I mean clearly it's very complicated.

NOTE Confidence: 0.883464144

00:05:51.230 --> 00:05:52.688 But you know,

NOTE Confidence: 0.883464144

00:05:52.688 --> 00:05:55.167 we know that you know studying

NOTE Confidence: 0.883464144

00:05:55.167 --> 00:05:56.862 gene expression looking at aspects

NOTE Confidence: 0.883464144

00:05:56.862 --> 00:05:58.389 of genetics of individuals,

NOTE Confidence: 0.883464144

00:05:58.390 --> 00:06:00.688 and I'll come back to epigenetic

NOTE Confidence: 0.883464144

00:06:00.688 --> 00:06:02.656 mechanisms that Marina mentioned that

NOTE Confidence: 0.883464144

00:06:02.656 --> 00:06:04.511 altogether this leads to changing

NOTE Confidence: 0.883464144

00:06:04.511 --> 00:06:06.680 proteins in the function and the

NOTE Confidence: 0.883464144

00:06:06.680 --> 00:06:08.860 phenotype of events of the disease so.

NOTE Confidence: 0.883464144

00:06:08.860 --> 00:06:11.100 That's where I'm going to start and

NOTE Confidence: 0.883464144

00:06:11.100 --> 00:06:13.294 and spend like the first few part.

NOTE Confidence: 0.883464144

00:06:13.294 --> 00:06:14.986 The first half I've been going

NOTE Confidence: 0.883464144

00:06:14.986 --> 00:06:17.200 north of my talk in terms of what

NOTE Confidence: 0.883464144

00:06:17.200 --> 00:06:18.927 have we learned about the human

NOTE Confidence: 0.883464144

00:06:18.927 --> 00:06:20.452 brain that guides our animal

NOTE Confidence: 0.883464144

00:06:20.452 --> 00:06:23.205 models to then see if we can start

NOTE Confidence: 0.883464144

00:06:23.205 --> 00:06:24.306 developing new treatments.

NOTE Confidence: 0.883464144

00:06:24.310 --> 00:06:26.325 So when we looked for

NOTE Confidence: 0.883464144

00:06:26.325 --> 00:06:28.340 example here in the striatum

NOTE Confidence: 0.822189974285714

00:06:28.425 --> 00:06:30.197 of human heroin users.

NOTE Confidence: 0.822189974285714

00:06:30.200 --> 00:06:34.830 Using approaches that were agnostic,

NOTE Confidence: 0.822189974285714

00:06:34.830 --> 00:06:38.100 Welsh and unbiased in a way of

NOTE Confidence: 0.822189974285714

00:06:38.100 --> 00:06:39.520 looking at thousands of genes,

NOTE Confidence: 0.822189974285714

00:06:39.520 --> 00:06:42.085 whether it initially was microarray

NOTE Confidence: 0.822189974285714

00:06:42.085 --> 00:06:44.650 strategies or more recently RNA

00:06:44.729 --> 00:06:47.177 sequencing of the transcriptome,

00:06:47.180 --> 00:06:50.491 we could see clearly that the gene

00:06:50.491 --> 00:06:52.462 expression signature inhering users

00:06:52.462 --> 00:06:54.966 differed from normal controls and

00:06:54.966 --> 00:06:57.576 where it differed was interesting

00:06:57.576 --> 00:07:00.100 because we saw much greater.

00:07:00.100 --> 00:07:02.570 This regulation of glutamatergic genes

00:07:02.570 --> 00:07:05.583 and perhaps not really surprising of

00:07:05.583 --> 00:07:07.928 the synaptic plasticity related genes.

00:07:07.930 --> 00:07:10.390 This the striatum receives really

00:07:10.390 --> 00:07:12.850 strong innovations from the prefrontal

00:07:12.928 --> 00:07:15.664 cortex and we know from a number of

00:07:15.664 --> 00:07:17.719 animal studies that that is really

00:07:17.720 --> 00:07:19.604 critical for especially aspects

00:07:19.604 --> 00:07:22.430 of even of drug seeking behavior.

00:07:22.430 --> 00:07:25.358 But we were surprised when we saw these

NOTE Confidence: 0.822189974285714

00:07:25.358 --> 00:07:27.699 really profound changes of epigenetics.

NOTE Confidence: 0.822189974285714

00:07:27.700 --> 00:07:29.228 And, importantly,

NOTE Confidence: 0.822189974285714

00:07:29.228 --> 00:07:33.048 these epigenetic marks were were.

NOTE Confidence: 0.822189974285714

00:07:33.050 --> 00:07:35.066 Opened up a new line of research for us,

NOTE Confidence: 0.822189974285714

00:07:35.070 --> 00:07:37.350 also in some aspects of our

NOTE Confidence: 0.822189974285714

00:07:37.350 --> 00:07:38.490 developmental cannabis studies.

NOTE Confidence: 0.822189974285714

00:07:38.490 --> 00:07:41.292 Because we focused a lot initially

NOTE Confidence: 0.822189974285714

00:07:41.292 --> 00:07:43.926 in trying to understand the

NOTE Confidence: 0.822189974285714

00:07:43.926 --> 00:07:45.978 individual vulnerability that.

NOTE Confidence: 0.822189974285714

00:07:45.980 --> 00:07:48.440 Why do some people?

NOTE Confidence: 0.822189974285714

00:07:48.440 --> 00:07:49.760 Many people may take a drug,

NOTE Confidence: 0.822189974285714

00:07:49.760 --> 00:07:51.495 but only a certain percentage

NOTE Confidence: 0.822189974285714

00:07:51.495 --> 00:07:53.230 may develop that disorder and

NOTE Confidence: 0.822189974285714

00:07:53.294 --> 00:07:55.119 we focus initially on genetics.

NOTE Confidence: 0.822189974285714

00:07:55.120 --> 00:07:58.096 But the environment of this complex

00:07:58.096 --> 00:08:00.680 disorder addiction plays a critical

00:08:00.680 --> 00:08:03.440 role and it plays a critical role in

00:08:03.440 --> 00:08:06.108 being able to change gene expression.

00:08:06.110 --> 00:08:08.354 And and in fact sometimes can

00:08:08.354 --> 00:08:09.850 override these genetic blueprints.

00:08:09.850 --> 00:08:11.691 So genes that should be closed are

00:08:11.691 --> 00:08:13.821 now turned on and genes that are that

00:08:13.821 --> 00:08:15.990 should be turned on and now turned off.

00:08:15.990 --> 00:08:19.570 And there are numerous epigenetic

00:08:19.570 --> 00:08:21.434 Marks and epigenetic mechanisms.

00:08:21.434 --> 00:08:22.366 Trust me,

00:08:22.370 --> 00:08:24.280 we've only touching the surface

00:08:24.280 --> 00:08:25.808 of it right now,

00:08:25.810 --> 00:08:28.042 but we had a fundamental understanding

00:08:28.042 --> 00:08:30.432 of what some of these epigenetic

00:08:30.432 --> 00:08:33.330 marks may mean on a functional level.

NOTE Confidence: 0.822189974285714

00:08:33.330 --> 00:08:36.249 So, for example, if you have methylation.

NOTE Confidence: 0.822189974285714

00:08:36.250 --> 00:08:39.046 DNA often that was a repressive

NOTE Confidence: 0.822189974285714

00:08:39.046 --> 00:08:41.802 mark and would reduce transcription,

NOTE Confidence: 0.822189974285714

00:08:41.802 --> 00:08:43.830 while for example,

NOTE Confidence: 0.822189974285714

00:08:43.830 --> 00:08:46.006 assimilation of the histones

NOTE Confidence: 0.822189974285714

00:08:46.006 --> 00:08:49.270 around that wrap around the DNA,

NOTE Confidence: 0.822189974285714

00:08:49.270 --> 00:08:52.066 the DNA wrapped around these histone

NOTE Confidence: 0.822189974285714

00:08:52.066 --> 00:08:53.930 proteins that regulate transcription

NOTE Confidence: 0.822189974285714

00:08:53.994 --> 00:08:55.809 and assimilation would open up

NOTE Confidence: 0.822189974285714

00:08:55.809 --> 00:08:58.068 those the those regions of the

NOTE Confidence: 0.822189974285714

00:08:58.068 --> 00:08:59.928 gene and turn on transcription.

NOTE Confidence: 0.822189974285714

00:08:59.930 --> 00:09:01.295 And depending on where methylation

NOTE Confidence: 0.822189974285714

00:09:01.295 --> 00:09:02.114 of histones occur,

NOTE Confidence: 0.822189974285714

00:09:02.120 --> 00:09:05.395 you could also have transcriptional

NOTE Confidence: 0.822189974285714

00:09:05.395 --> 00:09:06.050 repression.

NOTE Confidence: 0.822189974285714

00:09:06.050 --> 00:09:08.498 And what we saw in the brains of heroin

NOTE Confidence: 0.822189974285714

00:09:08.498 --> 00:09:11.017 users in Australia and predicted in

NOTE Confidence: 0.822189974285714

00:09:11.017 --> 00:09:13.197 particular of these epigenetic remodelers,

NOTE Confidence: 0.822189974285714

00:09:13.200 --> 00:09:15.285 it was predictive of this

NOTE Confidence: 0.822189974285714

00:09:15.285 --> 00:09:16.536 enhanced transcriptional state.

NOTE Confidence: 0.822189974285714

00:09:16.540 --> 00:09:21.430 But it was specific to certain gene.

NOTE Confidence: 0.822189974285714

00:09:21.430 --> 00:09:23.945 Gene regulators and often came

NOTE Confidence: 0.822189974285714

00:09:23.945 --> 00:09:26.460 back to the synaptic plasticity,

NOTE Confidence: 0.822189974285714

00:09:26.460 --> 00:09:28.100 so these epigenetic marks

NOTE Confidence: 0.822189974285714

00:09:28.100 --> 00:09:29.740 would correlate very strongly.

NOTE Confidence: 0.822189974285714

00:09:29.740 --> 00:09:32.132 Inherent users with glutamatergic

NOTE Confidence: 0.822189974285714

00:09:32.132 --> 00:09:35.122 genes or synaptic plasticity genes

NOTE Confidence: 0.822189974285714

00:09:35.122 --> 00:09:39.038 and it was very specific where these

NOTE Confidence: 0.822189974285714

00:09:39.038 --> 00:09:41.729 epigenetic tags were predicted to occur,

NOTE Confidence: 0.822189974285714

00:09:41.729 --> 00:09:44.130 and a lot of the the genetic

NOTE Confidence: 0.822189974285714

00:09:44.202 --> 00:09:46.846 changes related to, for example,

NOTE Confidence: 0.822189974285714

00:09:46.846 --> 00:09:49.418 a civilation and assimilation

NOTE Confidence: 0.822189974285714

00:09:49.418 --> 00:09:51.990 of the the lysine.

NOTE Confidence: 0.822189974285714

00:09:51.990 --> 00:09:52.695 In a region,

NOTE Confidence: 0.822189974285714

00:09:52.695 --> 00:09:54.737 and I'm not going to get too detail

NOTE Confidence: 0.822189974285714

00:09:54.737 --> 00:09:57.455 on the molecular related to enhancer

NOTE Confidence: 0.822189974285714

00:09:57.455 --> 00:10:00.905 regulation of gene transcription and it

NOTE Confidence: 0.822189974285714

00:10:00.905 --> 00:10:04.060 related to their years of heroin use.

NOTE Confidence: 0.822189974285714

00:10:04.060 --> 00:10:06.904 We were able to look at this in many

NOTE Confidence: 0.822189974285714

00:10:06.904 --> 00:10:09.020 different using many different techniques,

NOTE Confidence: 0.822189974285714

00:10:09.020 --> 00:10:11.270 and we saw consistently this.

NOTE Confidence: 0.89750624

00:10:11.270 --> 00:10:15.438 This opening of the transcriptome in in

NOTE Confidence: 0.89750624

00:10:15.438 --> 00:10:17.426 relation to the years of heroin news

NOTE Confidence: 0.89750624

00:10:17.426 --> 00:10:19.840 and especially cassette around these

NOTE Confidence: 0.89750624

00:10:19.840 --> 00:10:21.908 synaptic plasticity related genes.

NOTE Confidence: 0.89750624

00:10:21.910 --> 00:10:23.611 But because humans have such a very

NOTE Confidence: 0.89750624

00:10:23.611 --> 00:10:25.765 life and we don't know that much about

NOTE Confidence: 0.89750624

00:10:25.765 --> 00:10:27.479 all their lives just about their

NOTE Confidence: 0.89750624

00:10:27.479 --> 00:10:29.207 toxicology and often like I said,

NOTE Confidence: 0.89750624

00:10:29.210 --> 00:10:30.841 some of the people we knew their

NOTE Confidence: 0.89750624

00:10:30.841 --> 00:10:32.259 history of of hearing news,

NOTE Confidence: 0.89750624

00:10:32.260 --> 00:10:34.724 we use our animal models where animals

NOTE Confidence: 0.89750624

00:10:34.724 --> 00:10:36.882 will self administer heroin and we

NOTE Confidence: 0.89750624

00:10:36.882 --> 00:10:38.958 could actually replicate where in the

NOTE Confidence: 0.89750624

00:10:38.958 --> 00:10:41.216 genome or in the in the transcription.

NOTE Confidence: 0.89750624

00:10:41.220 --> 00:10:43.159 Say that we saw this gene expression

NOTE Confidence: 0.89750624

00:10:43.159 --> 00:10:45.205 changes and when we looked at the

NOTE Confidence: 0.89750624

00:10:45.205 --> 00:10:46.655 epigenetic tags in these regions,

NOTE Confidence: 0.89750624

00:10:46.660 --> 00:10:49.300 they correlated exactly to what we saw in,

NOTE Confidence: 0.89750624

00:10:49.300 --> 00:10:50.246 for example,

NOTE Confidence: 0.89750624

00:10:50.246 --> 00:10:52.679 their civilation of these these

NOTE Confidence: 0.89750624

00:10:52.679 --> 00:10:55.374 synaptic plasticity related genes and

NOTE Confidence: 0.89750624

00:10:55.374 --> 00:10:58.559 this acetylation of lysine 27 and I'm

NOTE Confidence: 0.89750624

00:10:58.559 --> 00:11:01.365 I'm not getting as as detail I know

NOTE Confidence: 0.89750624

00:11:01.365 --> 00:11:04.467 because even more broad clinical audience.

NOTE Confidence: 0.89750624

00:11:04.470 --> 00:11:06.057 But what is?

NOTE Confidence: 0.89750624

00:11:06.057 --> 00:11:09.760 What does that epigenetic change really mean?

NOTE Confidence: 0.89750624

00:11:09.760 --> 00:11:12.640 So for for the the histones in terms

NOTE Confidence: 0.89750624

00:11:12.640 --> 00:11:16.561 of we have tags that are put on these

NOTE Confidence: 0.89750624

00:11:16.561 --> 00:11:19.960 histones and they're they're called writers.

NOTE Confidence: 0.89750624

00:11:19.960 --> 00:11:21.922 These enzymes and we have others

NOTE Confidence: 0.89750624

00:11:21.922 --> 00:11:23.860 that take the these tags off,

NOTE Confidence: 0.89750624

00:11:23.860 --> 00:11:26.844 and we then have a readers that must

NOTE Confidence: 0.89750624

00:11:26.844 --> 00:11:29.382 give information to the system as to

NOTE Confidence: 0.89750624

00:11:29.382 --> 00:11:31.324 what these signals mean, and and they're.

NOTE Confidence: 0.89750624

00:11:31.324 --> 00:11:33.195 As I said, they're called readers.

NOTE Confidence: 0.89750624

00:11:33.195 --> 00:11:35.370 And for assimilation the bromodomain

NOTE Confidence: 0.89750624

00:11:35.370 --> 00:11:36.820 are the readers.

NOTE Confidence: 0.89750624

00:11:36.820 --> 00:11:39.448 They bind these assimilated lysine residues,

NOTE Confidence: 0.89750624

00:11:39.450 --> 00:11:40.635 and there are.

NOTE Confidence: 0.89750624

00:11:40.635 --> 00:11:43.005 About four families of these BT.

NOTE Confidence: 0.89750624

00:11:43.010 --> 00:11:45.162 These bromodomain proteins 32,

NOTE Confidence: 0.89750624

00:11:45.162 --> 00:11:46.776 three and four.

NOTE Confidence: 0.89750624

00:11:46.780 --> 00:11:48.425 And there's also one in the testes,

NOTE Confidence: 0.89750624

00:11:48.430 --> 00:11:50.725 but we only have 3 at least so far

NOTE Confidence: 0.89750624

00:11:50.725 --> 00:11:52.889 that was identified in the brain,

NOTE Confidence: 0.89750624

00:11:52.890 --> 00:11:55.860 and these are expressed in numerous

NOTE Confidence: 0.89750624

00:11:55.860 --> 00:11:56.850 brain regions.

NOTE Confidence: 0.89750624

00:11:56.850 --> 00:11:57.754 BRD 2-3 and four.

NOTE Confidence: 0.89750624

00:11:57.754 --> 00:12:00.190 But when we look in the brains both in in

NOTE Confidence: 0.89750624

00:12:00.190 --> 00:12:02.549 human hair and users and and animal models,

NOTE Confidence: 0.89750624

00:12:02.550 --> 00:12:05.007 we didn't see changes in BRD two or three.

NOTE Confidence: 0.89750624

00:12:05.010 --> 00:12:08.597 What we saw were changes in beer D4 and

NOTE Confidence: 0.89750624

00:12:08.597 --> 00:12:11.519 in different cohorts that we study.

NOTE Confidence: 0.89750624

00:12:11.520 --> 00:12:11.958 So.

NOTE Confidence: 0.89750624

00:12:11.958 --> 00:12:14.586 The thing that was also fascinating

NOTE Confidence: 0.89750624

00:12:14.586 --> 00:12:17.308 for us was that the again,

NOTE Confidence: 0.89750624

00:12:17.310 --> 00:12:20.593 the changes in in BRD 4 correlated

NOTE Confidence: 0.89750624

00:12:20.593 --> 00:12:23.383 very strongly with synaptic markers

NOTE Confidence: 0.89750624

00:12:23.383 --> 00:12:26.608 of markers of synaptic plasticity,

NOTE Confidence: 0.89750624

00:12:26.610 --> 00:12:27.994 such as DLG 4,

NOTE Confidence: 0.89750624

00:12:27.994 --> 00:12:30.070 which is the gene that encodes

NOTE Confidence: 0.89750624

00:12:30.070 --> 00:12:33.780 PSD 95 this postsynaptic density.

NOTE Confidence: 0.89750624

00:12:33.780 --> 00:12:34.150 Proteins.

NOTE Confidence: 0.89750624

00:12:34.150 --> 00:12:34.890 So again,

NOTE Confidence: 0.89750624

00:12:34.890 --> 00:12:37.480 every single thing told us that there

NOTE Confidence: 0.89750624

00:12:37.550 --> 00:12:40.020 was something really interesting about

NOTE Confidence: 0.89750624

00:12:40.020 --> 00:12:43.184 the BRD 4, the Bromodomain readers.

00:12:43.184 --> 00:12:45.848 So the thing that's very important

00:12:45.848 --> 00:12:47.927 about epigenetics and and at

00:12:47.927 --> 00:12:50.272 least at the time when we started

00:12:50.272 --> 00:12:52.629 studying this was although now in

00:12:52.629 --> 00:12:55.184 neuroscience more and more focus is

00:12:55.184 --> 00:12:57.600 looking at epigenetic mechanisms.

00:12:57.600 --> 00:12:59.682 The greatest information that we know

00:12:59.682 --> 00:13:01.900 really comes from the cancer field.

00:13:01.900 --> 00:13:05.180 And there they've been able to identify many,

00:13:05.180 --> 00:13:07.030 many different.

00:13:09.890 --> 00:13:13.110 Chemicals that can inhibit specific

00:13:13.110 --> 00:13:15.698 epigenetic mechanisms or promote

00:13:15.698 --> 00:13:17.639 certain epigenetic mechanisms.

00:13:17.640 --> 00:13:20.058 Because the cancer is definitely a

00:13:20.058 --> 00:13:22.070 disorder of epigenetic gone awry,

00:13:22.070 --> 00:13:24.670 so we were able to leverage what was

NOTE Confidence: 0.878953266

00:13:24.670 --> 00:13:26.639 being developed at that time in terms

NOTE Confidence: 0.878953266

00:13:26.639 --> 00:13:28.854 of some of the the chemicals to see

NOTE Confidence: 0.878953266

00:13:28.854 --> 00:13:31.392 whether or not if we could inhibit BRD,

NOTE Confidence: 0.878953266

00:13:31.392 --> 00:13:33.989 we had hoped to inhibit bird for,

NOTE Confidence: 0.878953266

00:13:33.990 --> 00:13:34.850 specifically.

NOTE Confidence: 0.878953266

00:13:34.850 --> 00:13:39.834 Could that itself decrease or heroin self?

NOTE Confidence: 0.878953266

00:13:39.834 --> 00:13:41.544 Administration and at the time,

NOTE Confidence: 0.878953266

00:13:41.550 --> 00:13:43.554 the prototypical BRD inhibitor,

NOTE Confidence: 0.878953266

00:13:43.554 --> 00:13:46.560 they would promote it as BRD.

NOTE Confidence: 0.878953266

00:13:46.560 --> 00:13:47.376 4 inhibitor.

NOTE Confidence: 0.878953266

00:13:47.376 --> 00:13:49.824 It really was not selected because

NOTE Confidence: 0.878953266

00:13:49.824 --> 00:13:52.196 it also could bind to the R.

NOTE Confidence: 0.878953266

00:13:52.200 --> 00:13:53.541 D2 and D3,

NOTE Confidence: 0.878953266

00:13:53.541 --> 00:13:56.570 so we nevertheless looked at the JQ

NOTE Confidence: 0.878953266

00:13:56.570 --> 00:13:58.545 one was approachable the inhibitor

NOTE Confidence: 0.878953266

00:13:58.545 --> 00:14:01.440 at a time in our animal models,

NOTE Confidence: 0.878953266

00:14:01.440 --> 00:14:02.422 and interestingly,

NOTE Confidence: 0.878953266

00:14:02.422 --> 00:14:05.859 when we gave it into the striatum,

NOTE Confidence: 0.878953266

00:14:05.860 --> 00:14:08.602 we could reduce heroin self administration

NOTE Confidence: 0.878953266

00:14:08.602 --> 00:14:10.430 and heroin seeking behavior.

NOTE Confidence: 0.878953266

00:14:10.430 --> 00:14:12.654 But the goal long term goal is to

NOTE Confidence: 0.878953266

00:14:12.654 --> 00:14:14.849 be able to develop medications.

NOTE Confidence: 0.878953266

00:14:14.850 --> 00:14:16.698 So we we know we're not going to

NOTE Confidence: 0.878953266

00:14:16.698 --> 00:14:18.766 infuse it into the brain of of people,

NOTE Confidence: 0.878953266

00:14:18.770 --> 00:14:21.230 and so even giving it systemically,

NOTE Confidence: 0.878953266

00:14:21.230 --> 00:14:23.760 we could significantly reduce heroin

NOTE Confidence: 0.878953266

00:14:23.760 --> 00:14:26.930 self administration behavior in the animals.

NOTE Confidence: 0.878953266

00:14:26.930 --> 00:14:29.190 So.

NOTE Confidence: 0.878953266

00:14:29.190 --> 00:14:32.370 The the leveraging you know the

NOTE Confidence: 0.878953266

00:14:32.370 --> 00:14:34.120 looking at the postmortems brains

NOTE Confidence: 0.878953266

00:14:34.120 --> 00:14:36.657 of heroin users you were able to

NOTE Confidence: 0.878953266

00:14:36.657 --> 00:14:38.467 see that these epigenetic changes,

NOTE Confidence: 0.878953266

00:14:38.470 --> 00:14:40.620 especially those that related to

NOTE Confidence: 0.878953266

00:14:40.620 --> 00:14:43.660 genes as part of synaptic plasticity,

NOTE Confidence: 0.878953266

00:14:43.660 --> 00:14:45.570 especially these little mergent genes,

NOTE Confidence: 0.878953266

00:14:45.570 --> 00:14:46.743 they correlated significantly

NOTE Confidence: 0.878953266

00:14:46.743 --> 00:14:49.480 with the years of heroin use and

NOTE Confidence: 0.878953266

00:14:49.546 --> 00:14:51.846 inhibiting it we could inhibit

NOTE Confidence: 0.878953266

00:14:51.846 --> 00:14:53.226 harrowing self administration

NOTE Confidence: 0.878953266

00:14:53.226 --> 00:14:55.289 behavior and more importantly,

NOTE Confidence: 0.878953266

00:14:55.290 --> 00:14:56.628 heroin seeking behavior.

NOTE Confidence: 0.869300692166667

00:14:58.900 --> 00:15:01.378 Unfortunately we have tried for many

NOTE Confidence: 0.869300692166667

00:15:01.378 --> 00:15:05.069 years to try to develop a or to obtain

NOTE Confidence: 0.869300692166667

00:15:05.069 --> 00:15:07.847 even a specific beauty for inhibitor and

NOTE Confidence: 0.869300692166667

00:15:07.847 --> 00:15:11.220 we still have not been able to do that.

NOTE Confidence: 0.869300692166667

00:15:11.220 --> 00:15:14.640 So you know, I I feel every time I

NOTE Confidence: 0.869300692166667

00:15:14.740 --> 00:15:18.260 give these this talk of what our our,

NOTE Confidence: 0.869300692166667

00:15:18.260 --> 00:15:21.900 you know these BT family of inhibitors,

NOTE Confidence: 0.869300692166667

00:15:21.900 --> 00:15:23.028 how they're being developed

NOTE Confidence: 0.869300692166667

00:15:23.028 --> 00:15:24.156 in the cancer field.

NOTE Confidence: 0.869300692166667

00:15:24.160 --> 00:15:25.936 But we still have not been able to

NOTE Confidence: 0.869300692166667

00:15:25.936 --> 00:15:27.296 find some that actually penetrate

NOTE Confidence: 0.869300692166667

00:15:27.296 --> 00:15:29.012 the brain on these the BRD.

NOTE Confidence: 0.869300692166667

00:15:29.020 --> 00:15:32.506 What specific purity for inhibitors that

NOTE Confidence: 0.869300692166667

00:15:32.510 --> 00:15:35.030 passes the blood brain barrier effectively?

NOTE Confidence: 0.869300692166667

00:15:35.030 --> 00:15:37.640 And so we're still trying,

NOTE Confidence: 0.869300692166667

00:15:37.640 --> 00:15:39.566 but it's important to also emphasize

NOTE Confidence: 0.869300692166667

00:15:39.566 --> 00:15:41.794 that it's not only our group that

NOTE Confidence: 0.869300692166667

00:15:41.794 --> 00:15:43.838 has seen these changes in beard for

NOTE Confidence: 0.869300692166667

00:15:43.903 --> 00:15:46.008 relevant to substance use disorders,

NOTE Confidence: 0.869300692166667

00:15:46.010 --> 00:15:47.970 other groups have seen that.

NOTE Confidence: 0.869300692166667

00:15:47.970 --> 00:15:52.072 In fact you cocaine self administration will

NOTE Confidence: 0.869300692166667

00:15:52.072 --> 00:15:55.608 also increase variety for and inhibiting.

NOTE Confidence: 0.869300692166667

00:15:55.610 --> 00:15:57.955 Giving the JQ one inhibitor the B

NOTE Confidence: 0.869300692166667

00:15:57.955 --> 00:16:00.109 inhibitor also will decrease cocaine,

NOTE Confidence: 0.869300692166667

00:16:00.110 --> 00:16:01.615 place preference and cocaine self

NOTE Confidence: 0.869300692166667

00:16:01.615 --> 00:16:03.469 administration and I think that that's

NOTE Confidence: 0.869300692166667

00:16:03.469 --> 00:16:04.974 really important because when we

NOTE Confidence: 0.869300692166667

00:16:04.974 --> 00:16:06.448 think about substance use disorders

NOTE Confidence: 0.869300692166667

00:16:06.448 --> 00:16:08.224 often we think OK we must get the

NOTE Confidence: 0.869300692166667

00:16:08.224 --> 00:16:10.652 most selective thing or I think in

NOTE Confidence: 0.869300692166667

00:16:10.652 --> 00:16:13.437 psychiatry in general I think you know

NOTE Confidence: 0.869300692166667

00:16:13.437 --> 00:16:15.927 the the strongest antagonists of the

NOTE Confidence: 0.869300692166667

00:16:15.927 --> 00:16:18.428 dopamine receptor and and selectivity,

NOTE Confidence: 0.869300692166667

00:16:18.430 --> 00:16:20.922 but for substance use disorders we know

NOTE Confidence: 0.869300692166667

00:16:20.922 --> 00:16:23.588 that many people are polysubstance users.

NOTE Confidence: 0.869300692166667

00:16:23.590 --> 00:16:25.150 So for me the fact that

NOTE Confidence: 0.869300692166667

00:16:25.150 --> 00:16:26.190 we see some commonality.

NOTE Confidence: 0.869300692166667

00:16:26.190 --> 00:16:29.376 Between the different substances of abuse,

NOTE Confidence: 0.869300692166667

00:16:29.380 --> 00:16:31.774 I think it's important so you know

NOTE Confidence: 0.869300692166667

00:16:31.774 --> 00:16:33.588 we're still optimistic about BRD 4.

NOTE Confidence: 0.841385738333333

00:16:36.220 --> 00:16:38.758 I'm still saying on this this,

NOTE Confidence: 0.841385738333333

00:16:38.760 --> 00:16:40.340 you know, in developing medications

NOTE Confidence: 0.841385738333333

00:16:40.340 --> 00:16:41.920 based on what we've seen,

NOTE Confidence: 0.841385738333333

00:16:41.920 --> 00:16:43.390 the human brain and how

NOTE Confidence: 0.841385738333333

00:16:43.390 --> 00:16:44.860 animal models can help us,

NOTE Confidence: 0.841385738333333

00:16:44.860 --> 00:16:47.308 I'm still going to focus on aspects of

NOTE Confidence: 0.841385738333333

00:16:47.308 --> 00:16:49.120 epigenetics and synaptic plasticity,

NOTE Confidence: 0.841385738333333

00:16:49.120 --> 00:16:52.156 and the reason is once again.

NOTE Confidence: 0.841385738333333

00:16:52.160 --> 00:16:55.282 When we look at the the brains

NOTE Confidence: 0.841385738333333

00:16:55.282 --> 00:16:57.478 of heroin users, as I said,

NOTE Confidence: 0.841385738333333

00:16:57.478 --> 00:16:59.969 you know when we we looked at the

NOTE Confidence: 0.841385738333333

00:16:59.969 --> 00:17:01.629 gene expression that transcriptome

NOTE Confidence: 0.841385738333333

00:17:01.629 --> 00:17:04.919 we were able to see these epigenetic

NOTE Confidence: 0.841385738333333

00:17:04.920 --> 00:17:06.830 genes related to epigenetic mechanisms

NOTE Confidence: 0.841385738333333

00:17:06.830 --> 00:17:08.358 and the synaptic plasticity.

NOTE Confidence: 0.841385738333333

00:17:08.360 --> 00:17:10.672 But you can also look at the epigenome

NOTE Confidence: 0.841385738333333

00:17:10.672 --> 00:17:12.460 itself in an agnostic manner.

NOTE Confidence: 0.841385738333333

00:17:12.460 --> 00:17:14.782 You can actually sequence the the

NOTE Confidence: 0.841385738333333

00:17:14.782 --> 00:17:17.402 epigenome and you can do that with

NOTE Confidence: 0.841385738333333

00:17:17.402 --> 00:17:19.719 a technique called a taxi which is

NOTE Confidence: 0.841385738333333

00:17:19.793 --> 00:17:22.117 assay for transposase accessible.

NOTE Confidence: 0.841385738333333

00:17:22.120 --> 00:17:23.074 Something basically,

NOTE Confidence: 0.841385738333333

00:17:23.074 --> 00:17:25.936 you're looking at chromatin state looking

NOTE Confidence: 0.841385738333333

00:17:25.936 --> 00:17:28.850 at where in the where in the epigenome,

NOTE Confidence: 0.841385738333333

00:17:28.850 --> 00:17:31.070 maybe in the chromatin is open,

NOTE Confidence: 0.841385738333333

00:17:31.070 --> 00:17:34.122 and therefore would be associated with gene

NOTE Confidence: 0.841385738333333

00:17:34.122 --> 00:17:36.567 transactivation and where it may be closed.

NOTE Confidence: 0.841385738333333

00:17:36.570 --> 00:17:38.642 And importantly, it's agnostic,

NOTE Confidence: 0.841385738333333

00:17:38.642 --> 00:17:41.750 because normally when you look at

NOTE Confidence: 0.841385738333333

00:17:41.831 --> 00:17:44.514 the epigenetic tags you actually

NOTE Confidence: 0.841385738333333

00:17:44.514 --> 00:17:47.569 choose a specific epigenetic mark.

NOTE Confidence: 0.841385738333333

00:17:47.570 --> 00:17:48.632 So for example,

NOTE Confidence: 0.841385738333333

00:17:48.632 --> 00:17:50.048 we might have chosen,

NOTE Confidence: 0.841385738333333

00:17:50.050 --> 00:17:51.506 like acetylation of lysine.

NOTE Confidence: 0.841385738333333

00:17:51.506 --> 00:17:54.124 27 that we showed that was changed

NOTE Confidence: 0.841385738333333

00:17:54.124 --> 00:17:56.320 in the brains of heroin users,

NOTE Confidence: 0.841385738333333

00:17:56.320 --> 00:17:58.608 but we know it's the combination of a

NOTE Confidence: 0.841385738333333

00:17:58.608 --> 00:18:00.948 number of epigenetic marks that will lead

NOTE Confidence: 0.841385738333333

00:18:00.948 --> 00:18:03.164 to these changes in gene transcription

NOTE Confidence: 0.841385738333333

00:18:03.164 --> 00:18:04.964 and therefore obviously downstream

NOTE Confidence: 0.841385738333333

00:18:04.964 --> 00:18:07.682 changes in in protein and function.

NOTE Confidence: 0.841385738333333

00:18:07.682 --> 00:18:10.916 So if we look agnostically using this,

NOTE Confidence: 0.841385738333333

00:18:10.920 --> 00:18:13.993 a taxi that has actually been extremely

NOTE Confidence: 0.841385738333333

00:18:13.993 --> 00:18:16.435 informative and finding out where which

NOTE Confidence: 0.841385738333333

00:18:16.435 --> 00:18:19.427 loci where in the in the epigenome is

NOTE Confidence: 0.841385738333333

00:18:19.427 --> 00:18:22.295 most significantly changed with hearing news.

NOTE Confidence: 0.841385738333333

00:18:22.300 --> 00:18:22.936 And importantly,

NOTE Confidence: 0.841385738333333

00:18:22.936 --> 00:18:24.526 this technique allows a something

NOTE Confidence: 0.841385738333333

00:18:24.526 --> 00:18:26.177 for me that's important for

NOTE Confidence: 0.841385738333333

00:18:26.177 --> 00:18:27.469 studying the human brain.

NOTE Confidence: 0.841385738333333

00:18:27.470 --> 00:18:30.870 It uses very little tissue,

NOTE Confidence: 0.841385738333333

00:18:30.870 --> 00:18:33.723 and this way we can look at different cells.

NOTE Confidence: 0.841385738333333

00:18:33.730 --> 00:18:35.710 Cell types in the human brain.

NOTE Confidence: 0.841385738333333

00:18:35.710 --> 00:18:37.432 Here in this particular study we

NOTE Confidence: 0.841385738333333

00:18:37.432 --> 00:18:39.109 look mainly at neurons and glia,

NOTE Confidence: 0.841385738333333

00:18:39.110 --> 00:18:41.258 not looking at specific neurons and

NOTE Confidence: 0.841385738333333

00:18:41.258 --> 00:18:43.890 specific non glia non neuronal subtypes.

NOTE Confidence: 0.841385738333333

00:18:43.890 --> 00:18:46.590 But even in doing that it was able to help

00:18:46.658 --> 00:18:49.489 us a lot and it was able to help us in here.

00:18:49.490 --> 00:18:52.310 A previous student who's now.

00:18:52.310 --> 00:18:55.820 Going for his first independent position,

00:18:55.820 --> 00:18:59.951 America Avari in in using the taxi we could

00:18:59.951 --> 00:19:04.318 see that indeed we were able to dissociate.

00:19:04.320 --> 00:19:06.812 Which epigenetic signatures that

00:19:06.812 --> 00:19:09.304 dissociated neurons from glia.

00:19:09.310 --> 00:19:13.886 But we could also see those that dissociated.

00:19:13.890 --> 00:19:16.767 Up here with disorders heroin use this.

00:19:16.770 --> 00:19:18.744 The dissociated heroin use in neurons

00:19:18.744 --> 00:19:21.334 and what we saw specifically was that

00:19:21.334 --> 00:19:23.752 the gene ontology of where these

00:19:23.752 --> 00:19:25.913 epigenetic changes were occurring again

00:19:25.913 --> 00:19:28.445 shows really strong dysregulation on an

00:19:28.450 --> 00:19:31.610 epigenetic level of synaptic plasticity.

00:19:31.610 --> 00:19:32.301 Again,

NOTE Confidence: 0.841385738333333

00:19:32.301 --> 00:19:35.065 these little meteorologic postsynaptic

NOTE Confidence: 0.841385738333333

00:19:35.065 --> 00:19:37.426 density dendritic changes and

NOTE Confidence: 0.841385738333333

00:19:37.426 --> 00:19:39.866 what were the genes changed?

NOTE Confidence: 0.841385738333333

00:19:39.870 --> 00:19:42.080 The top gene was Finn.

NOTE Confidence: 0.841385738333333

00:19:42.080 --> 00:19:44.540 And that was fascinating for us,

NOTE Confidence: 0.841385738333333

00:19:44.540 --> 00:19:46.500 because we had never studied fan and

NOTE Confidence: 0.841385738333333

00:19:46.500 --> 00:19:48.049 obviously it yellow come to that.

NOTE Confidence: 0.841385738333333

00:19:48.050 --> 00:19:49.688 You guys have been studying it for

NOTE Confidence: 0.841385738333333

00:19:49.688 --> 00:19:53.065 a while and the thing also was

NOTE Confidence: 0.841385738333333

00:19:53.065 --> 00:19:55.389 that the this this.

NOTE Confidence: 0.841385738333333

00:19:55.390 --> 00:19:58.190 The epigenetic changes that we saw for Finn.

NOTE Confidence: 0.841385738333333

00:19:58.190 --> 00:20:01.109 It actually explained Signal 6 to 8%

NOTE Confidence: 0.937294331428571

00:20:01.110 --> 00:20:04.785 of the variance for identifying heroin users.

NOTE Confidence: 0.937294331428571

00:20:04.790 --> 00:20:07.220 We were able to to show that my student Tony

NOTE Confidence: 0.937294331428571

00:20:07.283 --> 00:20:09.715 Roman was able to show that it's functional.

NOTE Confidence: 0.937294331428571

00:20:09.720 --> 00:20:12.198 The change this this enhancer region that

NOTE Confidence: 0.937294331428571

00:20:12.198 --> 00:20:14.992 we saw had the greatest chromatin change

NOTE Confidence: 0.937294331428571

00:20:14.992 --> 00:20:18.243 in Harry Newsers in the stratum and we were

NOTE Confidence: 0.937294331428571

00:20:18.243 --> 00:20:20.949 able to see also that it was self specific,

NOTE Confidence: 0.937294331428571

00:20:20.950 --> 00:20:23.254 at least that we didn't see these changes

NOTE Confidence: 0.937294331428571

00:20:23.254 --> 00:20:26.626 in glia, but it was mainly in neurons.

NOTE Confidence: 0.937294331428571

00:20:26.630 --> 00:20:28.370 And So what is Finn?

NOTE Confidence: 0.937294331428571

00:20:28.370 --> 00:20:29.490 As I said, you know.

NOTE Confidence: 0.937294331428571

00:20:29.490 --> 00:20:34.200 For Yale, I know many of you Vandyke and

NOTE Confidence: 0.937294331428571

00:20:34.200 --> 00:20:38.275 and me had been studying fit in relation

NOTE Confidence: 0.937294331428571

00:20:38.275 --> 00:20:40.765 to Alzheimer's and alcohol use disorders.

NOTE Confidence: 0.937294331428571

00:20:40.770 --> 00:20:42.906 For me, even though we had been getting

NOTE Confidence: 0.937294331428571

00:20:42.906 --> 00:20:45.595 more and more interested in the postsynaptic

NOTE Confidence: 0.937294331428571

00:20:45.595 --> 00:20:47.685 density in the glutamatergic signaling.

NOTE Confidence: 0.937294331428571

00:20:47.690 --> 00:20:50.290 Based on our postmortem results,

NOTE Confidence: 0.937294331428571

00:20:50.290 --> 00:20:52.264 it was interesting because we've never looked

NOTE Confidence: 0.937294331428571

00:20:52.264 --> 00:20:54.726 at fit and finish a stark tyrosine kinase,

NOTE Confidence: 0.937294331428571

00:20:54.730 --> 00:20:56.650 and it is a member of this group.

NOTE Confidence: 0.937294331428571

00:20:56.650 --> 00:20:59.575 Detergent, postsynaptic density and it

NOTE Confidence: 0.937294331428571

00:20:59.575 --> 00:21:01.915 regulates the cytoarchitecture dynamics.

NOTE Confidence: 0.937294331428571

00:21:01.920 --> 00:21:04.080 And we've found this in the

NOTE Confidence: 0.937294331428571

00:21:04.080 --> 00:21:04.800 nucleus accumbens,

NOTE Confidence: 0.937294331428571

00:21:04.800 --> 00:21:06.960 but my student run the Ellis also in

NOTE Confidence: 0.937294331428571

00:21:06.960 --> 00:21:08.640 using machine learning strategies,

NOTE Confidence: 0.937294331428571

00:21:08.640 --> 00:21:10.232 and I'll come to that a little later

NOTE Confidence: 0.937294331428571

00:21:10.232 --> 00:21:11.738 in the orbital frontal cortex.

NOTE Confidence: 0.937294331428571

00:21:11.740 --> 00:21:14.362 Another brain region critical in substance

NOTE Confidence: 0.937294331428571

00:21:14.362 --> 00:21:17.196 use disorders also identified as being

NOTE Confidence: 0.937294331428571

00:21:17.196 --> 00:21:21.359 part of a network predictive of heroin users.

NOTE Confidence: 0.937294331428571

00:21:21.360 --> 00:21:23.260 So in looking at Finn,

NOTE Confidence: 0.937294331428571

00:21:23.260 --> 00:21:26.196 we not only saw fin changes on the

NOTE Confidence: 0.937294331428571

00:21:26.196 --> 00:21:26.930 epigenetic level.

NOTE Confidence: 0.937294331428571

00:21:26.930 --> 00:21:29.122 We also saw it on the gene expression

NOTE Confidence: 0.937294331428571

00:21:29.122 --> 00:21:30.689 level in in the striatum.

NOTE Confidence: 0.937294331428571

00:21:30.690 --> 00:21:33.056 We saw it also change in animals

NOTE Confidence: 0.937294331428571

00:21:33.056 --> 00:21:34.774 that self administered heroin and

NOTE Confidence: 0.937294331428571

00:21:34.774 --> 00:21:36.886 we also even saw it in animals that

NOTE Confidence: 0.937294331428571

00:21:36.886 --> 00:21:38.410 self administered heroin.

NOTE Confidence: 0.937294331428571

00:21:38.410 --> 00:21:40.160 It correlated with their harrowing

NOTE Confidence: 0.937294331428571

00:21:40.160 --> 00:21:42.286 intake because here and at least

NOTE Confidence: 0.937294331428571

00:21:42.286 --> 00:21:44.491 the animals we know exactly how much

NOTE Confidence: 0.937294331428571

00:21:44.491 --> 00:21:46.447 hearing they take over their lives.

NOTE Confidence: 0.937294331428571

00:21:46.450 --> 00:21:49.817 We also saw it in cell cultures

NOTE Confidence: 0.937294331428571

00:21:49.817 --> 00:21:51.260 in with morphine.

NOTE Confidence: 0.937294331428571

00:21:51.260 --> 00:21:53.090 So.

NOTE Confidence: 0.937294331428571

00:21:53.090 --> 00:21:54.990 Thin as a kinase,

NOTE Confidence: 0.937294331428571

00:21:54.990 --> 00:21:56.890 it's activity in regulating

00:21:56.890 --> 00:21:58.883 downstream signaling relates to

00:21:58.883 --> 00:22:01.293 it being an phosphorylated and

00:22:01.293 --> 00:22:03.180 its phosphorylated active form.

00:22:03.180 --> 00:22:06.284 Inherent users was significantly

00:22:06.284 --> 00:22:08.352 increased as compared to the

00:22:08.352 --> 00:22:09.967 inactive form of first decreased.

00:22:09.970 --> 00:22:11.990 And indeed spin correlated with

00:22:11.990 --> 00:22:14.819 the years of heroin use in humans.

00:22:14.820 --> 00:22:15.934 So altogether,

00:22:15.934 --> 00:22:21.610 Finn was became very interesting for us and.

00:22:21.610 --> 00:22:25.290 As I mentioned, many people as I said,

00:22:25.290 --> 00:22:28.146 including you know a lot of the colleagues,

00:22:28.150 --> 00:22:30.580 your colleagues you know had shown

00:22:30.580 --> 00:22:33.352 Finn related to aspects of Alzheimer's

00:22:33.352 --> 00:22:36.042 because Finn phosphorylates the important

00:22:36.042 --> 00:22:38.568 downstream target of Finn is Tau,

00:22:38.570 --> 00:22:41.000 and hyperphosphorylated Tau is a

00:22:41.000 --> 00:22:42.944 pathological feature of Alzheimer's

00:22:42.944 --> 00:22:45.644 and another among other tauopathies,

00:22:45.644 --> 00:22:48.206 these neurodegenerative disorders.

00:22:48.206 --> 00:22:50.920 And years before we had seen

00:22:50.920 --> 00:22:52.036 these epigenetic changes,

00:22:52.040 --> 00:22:54.926 we had actually seen increase phosphorylate.

00:22:54.930 --> 00:22:56.340 Towel in the brains of heroin.

00:22:56.340 --> 00:23:00.360 Users in streaming, especially in Cortex.

00:23:00.360 --> 00:23:03.300 So the question is, you know,

00:23:03.300 --> 00:23:05.226 can you see the same things in animal models?

00:23:05.230 --> 00:23:06.166 So because humans,

00:23:06.166 --> 00:23:08.743 and especially I'd said at the time when

00:23:08.743 --> 00:23:10.717 we had found the increased phosphorylated

00:23:10.717 --> 00:23:13.363 Tau in the brains of heroin users

NOTE Confidence: 0.937294331428571

00:23:13.363 --> 00:23:15.353 before we started studying epigenetics,

NOTE Confidence: 0.937294331428571

00:23:15.360 --> 00:23:17.205 I thought that they had just hit their hats

NOTE Confidence: 0.937294331428571

00:23:17.205 --> 00:23:18.737 because you know when they're toxicated,

NOTE Confidence: 0.727810328181818

00:23:18.740 --> 00:23:20.284 maybe they had fallen.

NOTE Confidence: 0.727810328181818

00:23:20.284 --> 00:23:23.120 But we when animals self administered heroin,

NOTE Confidence: 0.727810328181818

00:23:23.120 --> 00:23:26.240 in addition to seeing increased fan it also.

NOTE Confidence: 0.727810328181818

00:23:26.240 --> 00:23:27.960 They also had hyperphosphorylated

NOTE Confidence: 0.727810328181818

00:23:27.960 --> 00:23:30.540 Tau that we could also replicate.

NOTE Confidence: 0.727810328181818

00:23:30.540 --> 00:23:33.347 You are in our cell culture model.

NOTE Confidence: 0.727810328181818

00:23:33.350 --> 00:23:33.970 Importantly,

NOTE Confidence: 0.727810328181818

00:23:33.970 --> 00:23:36.450 thin phosphorylated Tau phosphorylates

NOTE Confidence: 0.727810328181818

00:23:36.450 --> 00:23:39.950 toward a specific sites on Tau,

NOTE Confidence: 0.727810328181818

00:23:39.950 --> 00:23:42.821 and when you look at other sites that are

NOTE Confidence: 0.727810328181818

00:23:42.821 --> 00:23:44.628 phosphorylated by other kinases and Tau,

NOTE Confidence: 0.727810328181818

00:23:44.630 --> 00:23:46.190 we did not see those changes,

NOTE Confidence: 0.727810328181818

00:23:46.190 --> 00:23:48.760 so there was for Tau.

NOTE Confidence: 0.727810328181818

00:23:48.760 --> 00:23:51.392 There were five specific changes in regard

NOTE Confidence: 0.727810328181818

00:23:51.392 --> 00:23:53.340 to its phosphorylation and function.

NOTE Confidence: 0.8638507

00:23:55.650 --> 00:23:59.616 So. When we see these changes and said,

NOTE Confidence: 0.8638507

00:23:59.620 --> 00:24:02.644 you know, many, many years ago we

NOTE Confidence: 0.8638507

00:24:02.644 --> 00:24:04.312 see these hyperphosphorylated towel

NOTE Confidence: 0.8638507

00:24:04.312 --> 00:24:06.924 and like I said, I brushed it away.

NOTE Confidence: 0.8638507

00:24:06.924 --> 00:24:09.030 We see these changes in regard

NOTE Confidence: 0.8638507

00:24:09.106 --> 00:24:11.041 now to these epigenetic changes

NOTE Confidence: 0.8638507

00:24:11.041 --> 00:24:13.839 that really is not due to hitting.

NOTE Confidence: 0.8638507

00:24:13.840 --> 00:24:16.258 You know people hitting their heads

NOTE Confidence: 0.8638507

00:24:16.258 --> 00:24:18.817 or you know taking other substances

NOTE Confidence: 0.8638507

00:24:18.817 --> 00:24:21.146 but might be very, you know,

NOTE Confidence: 0.8638507

00:24:21.146 --> 00:24:23.197 newer toxic because we could also see

NOTE Confidence: 0.8638507

00:24:23.197 --> 00:24:25.294 that as I said in our animal models,

NOTE Confidence: 0.8638507

00:24:25.300 --> 00:24:27.820 so is opioid use predictive?

NOTE Confidence: 0.8638507

00:24:27.820 --> 00:24:29.672 Often your Commissioner type

NOTE Confidence: 0.8638507

00:24:29.672 --> 00:24:31.987 and so my student Brandy.

NOTE Confidence: 0.8638507

00:24:31.990 --> 00:24:33.244 We've been looking at this in

NOTE Confidence: 0.8638507

00:24:33.244 --> 00:24:34.765 a number of ways and I'm only

NOTE Confidence: 0.8638507

00:24:34.765 --> 00:24:36.037 going to show like one thing.

NOTE Confidence: 0.8638507

00:24:36.040 --> 00:24:39.764 So if we look at electronic health

NOTE Confidence: 0.8638507

00:24:39.764 --> 00:24:43.109 records and track opioid exposure.

NOTE Confidence: 0.8638507

00:24:43.110 --> 00:24:46.379 And your cognitive diagnosis later in life.

NOTE Confidence: 0.8638507

00:24:46.380 --> 00:24:47.994 Indeed, we actually see that if

NOTE Confidence: 0.8638507

00:24:47.994 --> 00:24:50.098 we look at people and look at we

NOTE Confidence: 0.8638507

00:24:50.098 --> 00:24:51.550 and if anybody wants to know,

NOTE Confidence: 0.8638507

00:24:51.550 --> 00:24:54.091 we can talk about it and the

NOTE Confidence: 0.8638507

00:24:54.091 --> 00:24:55.686 Q eight time period.

NOTE Confidence: 0.8638507

00:24:55.686 --> 00:24:57.851 But in looking at retrospectively

NOTE Confidence: 0.8638507

00:24:57.851 --> 00:25:01.002 and looking at 5 and 10 year

NOTE Confidence: 0.8638507

00:25:01.002 --> 00:25:02.778 follow-up following opioid exposure,

NOTE Confidence: 0.8638507

00:25:02.780 --> 00:25:05.405 we could see that indeed those individuals

NOTE Confidence: 0.8638507

00:25:05.405 --> 00:25:07.399 that had substance use disorder,

NOTE Confidence: 0.8638507

00:25:07.400 --> 00:25:09.600 especially opiate use disorder.

NOTE Confidence: 0.8638507

00:25:09.600 --> 00:25:11.800 It increased their diagnosis

NOTE Confidence: 0.8638507

00:25:11.800 --> 00:25:13.698 for neurocognitive their

NOTE Confidence: 0.8638507

00:25:13.698 --> 00:25:15.138 neurocognitive diagnosis.

NOTE Confidence: 0.8638507

00:25:15.140 --> 00:25:17.380 Later on in life.

NOTE Confidence: 0.8638507

00:25:17.380 --> 00:25:21.516 So, but back to our final story so.

NOTE Confidence: 0.8638507

00:25:21.520 --> 00:25:23.998 In animals, such self administered heroin,

NOTE Confidence: 0.8638507

00:25:24.000 --> 00:25:25.540 just like our heroin users.

NOTE Confidence: 0.8638507

00:25:25.540 --> 00:25:26.359 Like I said,

NOTE Confidence: 0.8638507

00:25:26.359 --> 00:25:28.270 we saw this increase in Finn and

NOTE Confidence: 0.8638507

00:25:28.339 --> 00:25:30.383 it made us interested to think of

NOTE Confidence: 0.8638507

00:25:30.383 --> 00:25:32.657 whether or not Finn may be important,

NOTE Confidence: 0.8638507

00:25:32.660 --> 00:25:34.970 for indeed directly causally regulating

NOTE Confidence: 0.8638507

00:25:34.970 --> 00:25:36.818 heroin self administration behavior.

NOTE Confidence: 0.8638507

00:25:36.820 --> 00:25:37.388 So we,

NOTE Confidence: 0.8638507

00:25:37.388 --> 00:25:39.092 we changed the expression of Finn

NOTE Confidence: 0.8638507

00:25:39.092 --> 00:25:41.230 by using viral media to minute

NOTE Confidence: 0.8638507

00:25:41.230 --> 00:25:42.738 manipulations and the animals,

NOTE Confidence: 0.8638507

00:25:42.740 --> 00:25:44.096 and we could see that indeed,

NOTE Confidence: 0.8638507

00:25:44.100 --> 00:25:45.540 if you're not down Finn,

NOTE Confidence: 0.8638507

00:25:45.540 --> 00:25:48.320 you could actually reduce heroin

NOTE Confidence: 0.8638507

00:25:48.320 --> 00:25:51.100 seeking behavior in these animals.

NOTE Confidence: 0.8638507

00:25:51.100 --> 00:25:54.352 But since our long term goal

NOTE Confidence: 0.8638507

00:25:54.352 --> 00:25:55.978 is medication development,

NOTE Confidence: 0.8638507

00:25:55.980 --> 00:25:58.234 we wanted to see whether or not

NOTE Confidence: 0.8638507

00:25:58.234 --> 00:25:59.200 a pharmacological inhibition

NOTE Confidence: 0.8638507

00:25:59.262 --> 00:26:00.497 of fan could also work,

NOTE Confidence: 0.8638507

00:26:00.500 --> 00:26:04.683 and there now this time we are lucky

NOTE Confidence: 0.8638507

00:26:04.683 --> 00:26:06.969 because then there was a inhibitor

NOTE Confidence: 0.8638507

00:26:06.969 --> 00:26:09.620 offence or ketamine that was being

NOTE Confidence: 0.8638507

00:26:09.620 --> 00:26:11.376 tested in Alzheimer's disease,

NOTE Confidence: 0.8638507

00:26:11.380 --> 00:26:13.468 and so we could use it in our animal

NOTE Confidence: 0.8638507

00:26:13.468 --> 00:26:15.322 models and we really made sure

NOTE Confidence: 0.8638507

00:26:15.322 --> 00:26:16.887 that animals were quite motivated.

NOTE Confidence: 0.8638507

00:26:16.890 --> 00:26:18.906 We increased increasing the work effort

NOTE Confidence: 0.8638507

00:26:18.906 --> 00:26:21.390 for them to self administer heroin.

NOTE Confidence: 0.8638507

00:26:21.390 --> 00:26:22.930 And then gave them sarcasm.

NOTE Confidence: 0.8638507

00:26:22.930 --> 00:26:24.340 And during those days that

NOTE Confidence: 0.8638507

00:26:24.340 --> 00:26:25.468 they have received sarcastic,

NOTE Confidence: 0.8638507

00:26:25.470 --> 00:26:28.506 it had reduced their currency and

NOTE Confidence: 0.8638507

00:26:28.506 --> 00:26:30.024 self administration behavior.

NOTE Confidence: 0.8638507

00:26:30.030 --> 00:26:32.322 In your when you're trying to

NOTE Confidence: 0.8638507

00:26:32.322 --> 00:26:33.850 develop medications for substance

NOTE Confidence: 0.8638507

00:26:33.916 --> 00:26:35.916 use disorders is really critical.

NOTE Confidence: 0.8638507

00:26:35.920 --> 00:26:38.662 Not to impact all aspects of

NOTE Confidence: 0.8638507

00:26:38.662 --> 00:26:40.666 their reward because, you know,

NOTE Confidence: 0.8638507

00:26:40.666 --> 00:26:43.200 we need to still have a regular

NOTE Confidence: 0.8638507

00:26:43.274 --> 00:26:44.360 hypnotic state.

NOTE Confidence: 0.8638507

00:26:44.360 --> 00:26:46.425 And when we gave a sarcastic name

NOTE Confidence: 0.8638507

00:26:46.425 --> 00:26:48.500 while their self administering food,

NOTE Confidence: 0.8638507

00:26:48.500 --> 00:26:51.909 for example, it didn't change that behavior.

NOTE Confidence: 0.8638507

00:26:51.910 --> 00:26:54.286 So when we look at the the human brain

NOTE Confidence: 0.8638507

00:26:54.286 --> 00:26:56.628 and our translational animal models,

NOTE Confidence: 0.8638507

00:26:56.630 --> 00:26:59.096 we see that there are specific

NOTE Confidence: 0.8638507

00:26:59.096 --> 00:27:00.740 epidemic and synaptic dysregulation,

NOTE Confidence: 0.8638507

00:27:00.740 --> 00:27:02.970 and a lot of that synaptic

NOTE Confidence: 0.8638507

00:27:02.970 --> 00:27:04.890 Goodman Turkic pathology.

NOTE Confidence: 0.8638507

00:27:04.890 --> 00:27:05.530 Really,

NOTE Confidence: 0.8638507

00:27:05.530 --> 00:27:07.819 the some of the targets that we

NOTE Confidence: 0.8638507

00:27:07.819 --> 00:27:09.875 have identified may be important

NOTE Confidence: 0.8638507

00:27:09.875 --> 00:27:11.378 for treatment development.

NOTE Confidence: 0.924738736

00:27:11.380 --> 00:27:13.440 But just as the epigenetic,

NOTE Confidence: 0.924738736

00:27:13.440 --> 00:27:16.221 the BRD the the Bromo domain family that we

NOTE Confidence: 0.924738736

00:27:16.221 --> 00:27:19.057 think is important for developing medication,

NOTE Confidence: 0.924738736

00:27:19.060 --> 00:27:21.596 others have and we saw and they saw

NOTE Confidence: 0.924738736

00:27:21.596 --> 00:27:23.209 other substances being impacted.

NOTE Confidence: 0.924738736

00:27:23.210 --> 00:27:26.201 It's like the the intake of other drugs.

NOTE Confidence: 0.924738736

00:27:26.201 --> 00:27:29.729 Other groups have been looking at then here

NOTE Confidence: 0.924738736

00:27:29.729 --> 00:27:33.021 dorid Bronze group at UCSF was able to see

NOTE Confidence: 0.924738736

00:27:33.021 --> 00:27:36.480 that in animals that are consumed alcohol,

NOTE Confidence: 0.924738736

00:27:36.480 --> 00:27:39.304 it also increased fat in the striatum and

NOTE Confidence: 0.924738736

00:27:39.304 --> 00:27:42.758 if they use their cabinet it could decrease

NOTE Confidence: 0.924738736

00:27:42.758 --> 00:27:45.270 the animals alcohol intake behavior.

NOTE Confidence: 0.924738736

00:27:45.270 --> 00:27:49.230 But at Yale, you guys have?

NOTE Confidence: 0.924738736

00:27:49.230 --> 00:27:50.838 They've been clinical studies,

NOTE Confidence: 0.924738736

00:27:50.838 --> 00:27:52.446 carried out with individuals,

NOTE Confidence: 0.924738736

00:27:52.450 --> 00:27:53.692 alcohol use disorder,

NOTE Confidence: 0.924738736

00:27:53.692 --> 00:27:56.176 and have not seen any significant

NOTE Confidence: 0.924738736

00:27:56.176 --> 00:27:58.308 changes with alcohol consumption.

NOTE Confidence: 0.924738736

00:27:58.310 --> 00:28:00.109 But it was really nice because it

NOTE Confidence: 0.924738736

00:28:00.109 --> 00:28:01.636 was a translational study and they

NOTE Confidence: 0.924738736

00:28:01.636 --> 00:28:03.267 also had a mouse model where they

NOTE Confidence: 0.924738736

00:28:03.320 --> 00:28:05.498 could see that perhaps perhaps the

NOTE Confidence: 0.924738736

00:28:05.498 --> 00:28:08.268 habitual responded for for ethanol,

NOTE Confidence: 0.924738736

00:28:08.270 --> 00:28:10.700 maybe what may be affected by

NOTE Confidence: 0.924738736

00:28:10.700 --> 00:28:13.208 our cabinet and there's and those

NOTE Confidence: 0.924738736

00:28:13.208 --> 00:28:15.228 of course may be important.

NOTE Confidence: 0.924738736

00:28:15.230 --> 00:28:18.266 So here we did not see, at least for alcohol.

NOTE Confidence: 0.924738736

00:28:18.266 --> 00:28:20.630 Just sort of carry that by.

NOTE Confidence: 0.924738736

00:28:20.630 --> 00:28:22.202 Work, you guys,

NOTE Confidence: 0.924738736

00:28:22.202 --> 00:28:24.298 that circadian pattern effect?

NOTE Confidence: 0.924738736

00:28:24.300 --> 00:28:26.351 But I think that there's still a

NOTE Confidence: 0.924738736

00:28:26.351 --> 00:28:28.391 long way because we still think then

NOTE Confidence: 0.924738736

00:28:28.391 --> 00:28:30.701 see on so many levels that thing is

NOTE Confidence: 0.924738736

00:28:30.701 --> 00:28:33.520 really important for a number of at

NOTE Confidence: 0.924738736

00:28:33.520 --> 00:28:36.238 least opiate use changes that we saw.

NOTE Confidence: 0.924738736

00:28:36.240 --> 00:28:38.704 So I'm gonna go back to the orbital

NOTE Confidence: 0.924738736

00:28:38.704 --> 00:28:40.596 frontal cortex where if you remember

NOTE Confidence: 0.924738736

00:28:40.596 --> 00:28:42.660 we had seen this changes in fan

NOTE Confidence: 0.924738736

00:28:42.660 --> 00:28:43.980 and the overall frontal cortex.

NOTE Confidence: 0.924738736

00:28:43.980 --> 00:28:45.244 As I said earlier,

NOTE Confidence: 0.924738736

00:28:45.244 --> 00:28:47.140 is is a critical brain region

NOTE Confidence: 0.924738736

00:28:47.210 --> 00:28:49.320 also for substance use disorder,

NOTE Confidence: 0.924738736

00:28:49.320 --> 00:28:51.905 especially in terms of guiding

NOTE Confidence: 0.924738736

00:28:51.905 --> 00:28:52.939 decision making.

NOTE Confidence: 0.924738736

49

00:28:52.940 --> 00:28:54.628 The values of reward,

NOTE Confidence: 0.924738736

00:28:54.628 --> 00:28:56.738 goal directed behavior and even

NOTE Confidence: 0.924738736

00:28:56.738 --> 00:28:59.430 in reversal learning aspects so.

NOTE Confidence: 0.924738736

00:28:59.430 --> 00:29:01.154 Although we saw Finn,

NOTE Confidence: 0.924738736

00:29:01.154 --> 00:29:03.309 Finn was not the primary.

NOTE Confidence: 0.924738736

00:29:03.310 --> 00:29:06.130 Significantly changed gene hub

NOTE Confidence: 0.924738736

00:29:06.130 --> 00:29:08.950 using machine learning approaches.

NOTE Confidence: 0.924738736

00:29:08.950 --> 00:29:12.720 It was shesa 7. And she's just seven.

NOTE Confidence: 0.924738736

00:29:12.720 --> 00:29:15.750 We solved that all models that Randy

NOTE Confidence: 0.924738736

00:29:15.750 --> 00:29:18.655 used and our colleagues in terms of

NOTE Confidence: 0.924738736

00:29:18.655 --> 00:29:21.078 machine learning models predicted

NOTE Confidence: 0.924738736

00:29:21.080 --> 00:29:24.278 so predicted that she's a seven

NOTE Confidence: 0.924738736

00:29:24.278 --> 00:29:27.940 was really key in dissociating.

NOTE Confidence: 0.924738736

00:29:27.940 --> 00:29:30.772 Differentiating the gene expression

NOTE Confidence: 0.924738736

00:29:30.772 --> 00:29:33.340 pattern of parent users from control.

NOTE Confidence: 0.924738736

00:29:33.340 --> 00:29:35.158 So basically that's what you're asking.

NOTE Confidence: 0.924738736

00:29:35.160 --> 00:29:37.836 You know, these machine learning algorithms,

NOTE Confidence: 0.924738736

00:29:37.840 --> 00:29:41.326 how? How well do these these?

NOTE Confidence: 0.924738736

00:29:41.330 --> 00:29:44.666 Transcriptional signatures tell you who's a.

NOTE Confidence: 0.924738736

00:29:44.670 --> 00:29:47.162 Maybe a heroin user and who is

NOTE Confidence: 0.924738736

00:29:47.162 --> 00:29:48.230 a control subject.

NOTE Confidence: 0.924738736

00:29:48.230 --> 00:29:49.230 And as I said,

NOTE Confidence: 0.924738736

00:29:49.230 --> 00:29:51.150 she's a 17 up all the time,

NOTE Confidence: 0.924738736

00:29:51.150 --> 00:29:53.690 so once she's a 7.

NOTE Confidence: 0.924738736

00:29:53.690 --> 00:29:56.810 It's usually 7 is an auxiliary

NOTE Confidence: 0.924738736

00:29:56.810 --> 00:29:58.890 subunit and the the.

NOTE Confidence: 0.924738736

00:29:58.890 --> 00:30:00.708 Unfortunate thing is that actually a

NOTE Confidence: 0.924738736

00:30:00.708 --> 00:30:02.989 good thing and an unfortunate thing.

NOTE Confidence: 0.924738736

00:30:02.990 --> 00:30:05.231 The good thing is that for us is that

NOTE Confidence: 0.924738736

00:30:05.231 --> 00:30:07.270 it's something novel because very,

NOTE Confidence: 0.924738736

00:30:07.270 --> 00:30:10.287 very few people have studied Chester 7.

NOTE Confidence: 0.924738736

00:30:10.290 --> 00:30:12.650 It's considered an auxiliary subunit,

NOTE Confidence: 0.924738736

00:30:12.650 --> 00:30:14.690 not only at the Ampang

NOTE Confidence: 0.924738736

00:30:14.690 --> 00:30:15.506 glutamatergic receptor,

NOTE Confidence: 0.924738736

00:30:15.510 --> 00:30:18.422 but even at the GABA a receptor

NOTE Confidence: 0.924738736

00:30:18.422 --> 00:30:19.670 and different researchers

NOTE Confidence: 0.924738736

00:30:19.745 --> 00:30:21.790 have evidence on both sides,

NOTE Confidence: 0.924738736

00:30:21.790 --> 00:30:24.758 so that's why we are working with the

NOTE Confidence: 0.924738736

00:30:24.758 --> 00:30:27.222 Yale your proteomics core and being

NOTE Confidence: 0.924738736

00:30:27.222 --> 00:30:30.560 able to see where is Jesus 7 binding,

NOTE Confidence: 0.924738736

00:30:30.560 --> 00:30:32.210 at least in our models,

NOTE Confidence: 0.924738736

00:30:32.210 --> 00:30:33.905 and so hopefully we'll be

NOTE Confidence: 0.924738736

00:30:33.905 --> 00:30:35.600 able to get some insights

NOTE Confidence: 0.906192348333333

00:30:35.671 --> 00:30:37.194 for that, but in the meantime,

NOTE Confidence: 0.906192348333333

00:30:37.194 --> 00:30:38.857 what we've done is to try to

NOTE Confidence: 0.906192348333333

00:30:38.857 --> 00:30:40.547 see is sheets of seven, really.

NOTE Confidence: 0.906192348333333

00:30:40.547 --> 00:30:42.338 Critical for parents,

NOTE Confidence: 0.906192348333333

00:30:42.338 --> 00:30:45.323 self administration and parents seeking

NOTE Confidence: 0.906192348333333

00:30:45.323 --> 00:30:47.468 behavior and here Randy and Jackie,

NOTE Confidence: 0.906192348333333

00:30:47.468 --> 00:30:49.470 Jackie Fuller and postdoc in a group.

NOTE Confidence: 0.906192348333333

00:30:49.470 --> 00:30:51.648 You could see that indeed it

NOTE Confidence: 0.906192348333333

00:30:51.648 --> 00:30:53.808 replicated that her she's a 70

NOTE Confidence: 0.906192348333333

00:30:53.808 --> 00:30:55.704 and the cohorts of heroin users

NOTE Confidence: 0.906192348333333

00:30:55.704 --> 00:30:57.690 is reduced in rats is reduced.

NOTE Confidence: 0.906192348333333

00:30:57.690 --> 00:30:59.694 But actually it correlates

NOTE Confidence: 0.906192348333333

00:30:59.694 --> 00:31:02.199 significantly with the the the

NOTE Confidence: 0.906192348333333

00:31:02.199 --> 00:31:04.719 rest heroin seeking behavior.

NOTE Confidence: 0.906192348333333

00:31:04.720 --> 00:31:08.136 So we could we wanted to see if

NOTE Confidence: 0.906192348333333

00:31:08.136 --> 00:31:10.876 overexpressing she's a seven could change

NOTE Confidence: 0.906192348333333

00:31:10.876 --> 00:31:13.582 was relevant to Q induced behavior

NOTE Confidence: 0.906192348333333

00:31:13.670 --> 00:31:16.376 so we had animals self administer

NOTE Confidence: 0.906192348333333

00:31:16.380 --> 00:31:19.686 heroin and also saline as comparison

NOTE Confidence: 0.906192348333333

00:31:19.686 --> 00:31:21.408 groups and then we overexpressed.

NOTE Confidence: 0.906192348333333

00:31:21.408 --> 00:31:23.713 She's a seven in the animals and we

NOTE Confidence: 0.906192348333333

00:31:23.713 --> 00:31:25.456 could see that in those animals that

NOTE Confidence: 0.906192348333333

00:31:25.456 --> 00:31:27.619 had heroin and she's the seven we can

NOTE Confidence: 0.906192348333333

00:31:27.619 --> 00:31:29.416 push that heroin seeking behavior.

NOTE Confidence: 0.906192348333333

00:31:29.416 --> 00:31:32.404 So she's a 7 augments human

NOTE Confidence: 0.906192348333333

00:31:32.404 --> 00:31:34.880 induced parents seeking behavior.

NOTE Confidence: 0.906192348333333

00:31:34.880 --> 00:31:35.984 As I mentioned,

NOTE Confidence: 0.906192348333333

00:31:35.984 --> 00:31:37.824 the orbital frontal cortex is

NOTE Confidence: 0.906192348333333

00:31:37.824 --> 00:31:39.809 important for reversal learning and

NOTE Confidence: 0.906192348333333

00:31:39.809 --> 00:31:42.179 indeed overexpressing she's a 7 in.

NOTE Confidence: 0.906192348333333

00:31:42.180 --> 00:31:44.432 Also change sucrose reversal

NOTE Confidence: 0.906192348333333

00:31:44.432 --> 00:31:47.247 learning so animals that first

NOTE Confidence: 0.906192348333333

00:31:47.247 --> 00:31:49.780 learn to self administer heroin,

NOTE Confidence: 0.906192348333333

00:31:49.780 --> 00:31:51.380 we would switch and give

NOTE Confidence: 0.906192348333333

00:31:51.380 --> 00:31:52.660 them a different reward.

NOTE Confidence: 0.906192348333333

00:31:52.660 --> 00:31:54.352 They're the conditions under which the

NOTE Confidence: 0.906192348333333

00:31:54.352 --> 00:31:56.408 levers and we could see that it was a.

NOTE Confidence: 0.906192348333333

00:31:56.410 --> 00:31:58.720 She's a 7 overexpression could

NOTE Confidence: 0.906192348333333

00:31:58.720 --> 00:32:00.568 promote reversal learning more

NOTE Confidence: 0.906192348333333

00:32:00.568 --> 00:32:02.400 versus the heroin animals.

NOTE Confidence: 0.906192348333333

00:32:02.400 --> 00:32:04.976 So the question is what is happening?

NOTE Confidence: 0.906192348333333

00:32:04.980 --> 00:32:07.976 In the brain, on a transcriptional level.

NOTE Confidence: 0.906192348333333

00:32:07.980 --> 00:32:09.456 With she's a 7.

NOTE Confidence: 0.906192348333333

00:32:09.456 --> 00:32:12.805 And so here what we did was to

NOTE Confidence: 0.906192348333333

00:32:12.805 --> 00:32:15.405 look at what gene expression

NOTE Confidence: 0.906192348333333

00:32:15.405 --> 00:32:17.918 patterns is similar in heroin,

NOTE Confidence: 0.906192348333333

00:32:17.918 --> 00:32:19.814 self administration and under

NOTE Confidence: 0.906192348333333

00:32:19.814 --> 00:32:21.710 conditions of no heroin,

NOTE Confidence: 0.906192348333333

00:32:21.710 --> 00:32:22.552 self administration.

NOTE Confidence: 0.906192348333333

00:32:22.552 --> 00:32:25.078 Just she's a 7 overexpression of

NOTE Confidence: 0.906192348333333

00:32:25.078 --> 00:32:27.039 the orbital frontal cortex and

NOTE Confidence: 0.906192348333333

00:32:27.039 --> 00:32:29.489 this is a strategy using rank rank.

NOTE Confidence: 0.906192348333333

00:32:29.490 --> 00:32:31.770 It's called hypergeometric overlap.

NOTE Confidence: 0.906192348333333

00:32:31.770 --> 00:32:35.190 In comparing 2 gene expression sets,

NOTE Confidence: 0.906192348333333

00:32:35.190 --> 00:32:36.614 it's a little convoluted.

NOTE Confidence: 0.906192348333333

00:32:36.614 --> 00:32:37.326 It's not,

NOTE Confidence: 0.906192348333333

00:32:37.330 --> 00:32:39.283 I mean that it's just the opposite

NOTE Confidence: 0.906192348333333

00:32:39.283 --> 00:32:40.120 in terms of.

NOTE Confidence: 0.906192348333333

00:32:40.120 --> 00:32:43.275 Where we see significant overlaps

NOTE Confidence: 0.906192348333333

00:32:43.275 --> 00:32:46.430 in genes that are downregulated

NOTE Confidence: 0.906192348333333

00:32:46.529 --> 00:32:48.857 in one comparison group.

NOTE Confidence: 0.906192348333333

00:32:48.860 --> 00:32:50.786 And over here these are genes

NOTE Confidence: 0.906192348333333

00:32:50.786 --> 00:32:51.749 that are upregulated,

NOTE Confidence: 0.906192348333333

00:32:51.750 --> 00:32:54.264 but there was a complete concordance

NOTE Confidence: 0.906192348333333

00:32:54.264 --> 00:32:56.902 between whether or not complete a

NOTE Confidence: 0.906192348333333

00:32:56.902 --> 00:32:59.107 very strong concordance between the

56

00:32:59.107 --> 00:33:01.904 gene genes that are upregulated in

00:33:01.904 --> 00:33:03.908 hiring users and those that are

00:33:03.908 --> 00:33:06.241 are also upregulated by she's a 7

00:33:06.241 --> 00:33:07.826 overexpression and the same thing.

00:33:07.830 --> 00:33:09.930 Those that are downregulated so there.

00:33:09.930 --> 00:33:11.154 This there is this.

00:33:11.154 --> 00:33:12.990 She's a 7 overexpression mimics a

00:33:13.055 --> 00:33:15.319 lot of the patterns in the in the

00:33:15.319 --> 00:33:17.421 orbital frontal cortex that we see

00:33:17.421 --> 00:33:18.893 with parents often ministration.

00:33:18.900 --> 00:33:22.330 So and not in the discordant genes.

00:33:22.330 --> 00:33:24.360 This is just the the odds ratio

00:33:24.360 --> 00:33:26.140 and this this significance.

00:33:26.140 --> 00:33:29.206 So what are the biological features

00:33:29.206 --> 00:33:32.829 that are that are changed in relation

00:33:32.829 --> 00:33:36.140 to the genes that are that she's

00:33:36.140 --> 00:33:37.400 a 7 regulates?

00:33:37.400 --> 00:33:39.806 Once again not surprising we see

00:33:39.806 --> 00:33:41.980 changes related to postsynaptic density,

00:33:41.980 --> 00:33:43.993 the synaptic plasticity,

00:33:43.993 --> 00:33:46.006 the cytoskeletal organization.

00:33:46.010 --> 00:33:49.699 Also we see a number of of

00:33:49.699 --> 00:33:51.730 of disorders related to,

00:33:51.730 --> 00:33:54.302 for example, Alzheimer's disease,

00:33:54.302 --> 00:33:55.588 Huntington's disease,

00:33:55.590 --> 00:33:57.468 these neurodegenerative disorders

00:33:57.468 --> 00:34:00.598 come into the gene transcriptional

00:34:00.598 --> 00:34:03.940 profile that she's a seven is inducing.

00:34:03.940 --> 00:34:06.300 And even going back to the machine learning,

00:34:06.300 --> 00:34:07.353 I'm not going to show a lot of it.

00:34:07.360 --> 00:34:09.064 We can see that other genes that have

NOTE Confidence: 0.91129993625

00:34:09.064 --> 00:34:10.298 been identified even though they were

NOTE Confidence: 0.91129993625

00:34:10.298 --> 00:34:11.740 not as strong as sheets of seven,

NOTE Confidence: 0.91129993625

00:34:11.740 --> 00:34:13.854 for example, here this product could here,

NOTE Confidence: 0.91129993625

00:34:13.860 --> 00:34:16.737 is it also in she's a 7.

NOTE Confidence: 0.91129993625

00:34:16.740 --> 00:34:18.828 And when you change she's a 7 expression.

NOTE Confidence: 0.91129993625

00:34:18.830 --> 00:34:20.979 It also changes a number of these

NOTE Confidence: 0.91129993625

00:34:20.979 --> 00:34:23.000 genes that the machine learning

NOTE Confidence: 0.91129993625

00:34:23.000 --> 00:34:26.766 strategies had shown to relate to heroin

NOTE Confidence: 0.91129993625

00:34:26.766 --> 00:34:29.730 seeking behavior in in particular.

NOTE Confidence: 0.91129993625

00:34:29.730 --> 00:34:32.760 So using these unbiased computational

NOTE Confidence: 0.91129993625

00:34:32.760 --> 00:34:36.330 strategies, we were able to

NOTE Confidence: 0.91129993625

00:34:36.330 --> 00:34:38.550 identify molecular alterations,

NOTE Confidence: 0.91129993625

00:34:38.550 --> 00:34:40.500 again emphasizing synaptic

NOTE Confidence: 0.91129993625

00:34:40.500 --> 00:34:43.750 dysregulation and also this aspect

NOTE Confidence: 0.91129993625

00:34:43.750 --> 00:34:46.869 of heightened neurocognitive risk.

NOTE Confidence: 0.87155301625

00:34:52.160 --> 00:34:55.896 So the last part of you know the

NOTE Confidence: 0.87155301625

00:34:55.900 --> 00:34:59.050 strategies that we've been using to try

NOTE Confidence: 0.87155301625

00:34:59.050 --> 00:35:02.280 to develop new treatments or potential

NOTE Confidence: 0.87155301625

00:35:02.280 --> 00:35:05.498 new treatments for opiate use disorder.

NOTE Confidence: 0.87155301625

00:35:05.498 --> 00:35:08.127 The first strategies, as I mentioned,

NOTE Confidence: 0.87155301625

00:35:08.127 --> 00:35:10.281 started with our human subjects and

NOTE Confidence: 0.87155301625

00:35:10.281 --> 00:35:12.570 looking at postmortem tissue and then

NOTE Confidence: 0.87155301625

00:35:12.570 --> 00:35:14.840 going to our preclinical animal models

NOTE Confidence: 0.87155301625

00:35:14.840 --> 00:35:16.922 and trying to manipulate them and

NOTE Confidence: 0.87155301625

00:35:16.922 --> 00:35:18.870 moving them into the clinical studies.

NOTE Confidence: 0.900633766666667

00:35:21.200 --> 00:35:25.790 What we are. Also did was using our

NOTE Confidence: 0.900633766666667

00:35:25.790 --> 00:35:28.817 animal models in general to see what

NOTE Confidence: 0.900633766666667

00:35:28.817 --> 00:35:32.313 they may help to identify and here this

NOTE Confidence: 0.900633766666667

00:35:32.313 --> 00:35:34.768 was an unusual start because we've

NOTE Confidence: 0.900633766666667

00:35:34.768 --> 00:35:36.448 been looking at the developmental

NOTE Confidence: 0.900633766666667

00:35:36.448 --> 00:35:38.438 effects of cannabis for many years,

00:35:38.440 --> 00:35:41.344 both from the prenatal and analysing

00:35:41.344 --> 00:35:45.019 exposure and we had looked in in humans

00:35:45.020 --> 00:35:47.365 in terms of fetal samples for example,

00:35:47.370 --> 00:35:49.002 but even our animal models because

00:35:49.002 --> 00:35:50.645 our animal models we could allow

00:35:50.645 --> 00:35:52.409 them to grow into adults and really

00:35:52.409 --> 00:35:54.050 see doesn't impact on behavior.

00:35:54.050 --> 00:35:55.760 And one behavior that we we spend a lot

00:35:55.760 --> 00:35:57.550 of time looking at because initially,

00:35:57.550 --> 00:35:59.490 especially with the adolescent exposure,

00:35:59.490 --> 00:36:02.610 was this gateway hypothesis of cannabis

00:36:02.610 --> 00:36:04.866 exposure increasing addiction risk even

00:36:04.866 --> 00:36:07.470 to other substances later in life.

00:36:07.470 --> 00:36:10.956 And here we looked at opioids and.

00:36:10.960 --> 00:36:12.760 And then we can go into QA as to

00:36:12.760 --> 00:36:14.189 why we looked at opioids,

NOTE Confidence: 0.900633766666667

00:36:14.190 --> 00:36:17.030 but there is a they share a number

NOTE Confidence: 0.900633766666667

00:36:17.030 --> 00:36:19.825 of signaling mechanisms with the

NOTE Confidence: 0.900633766666667

00:36:19.825 --> 00:36:21.829 endogenous cannabinoid receptors.

NOTE Confidence: 0.900633766666667

00:36:21.830 --> 00:36:24.322 And we could see in animals that

NOTE Confidence: 0.900633766666667

00:36:24.322 --> 00:36:26.770 had been exposed to THC prenatally,

NOTE Confidence: 0.900633766666667

00:36:26.770 --> 00:36:29.035 that they would self administer

NOTE Confidence: 0.900633766666667

00:36:29.035 --> 00:36:30.847 heroin more than controls,

NOTE Confidence: 0.900633766666667

00:36:30.850 --> 00:36:32.130 and even on their conditions,

NOTE Confidence: 0.900633766666667

00:36:32.130 --> 00:36:33.640 when they we had them,

NOTE Confidence: 0.900633766666667

00:36:33.640 --> 00:36:35.728 they would take the same amount of heroin.

NOTE Confidence: 0.900633766666667

00:36:35.730 --> 00:36:38.258 If you just looked at even the first,

NOTE Confidence: 0.900633766666667

00:36:38.260 --> 00:36:40.913 they're running to the first letter lever

NOTE Confidence: 0.900633766666667

00:36:40.913 --> 00:36:43.988 to get that first hit of of of heroin.

NOTE Confidence: 0.900633766666667

00:36:43.990 --> 00:36:46.666 In those adult animals, with penalty, etc.

NOTE Confidence: 0.900633766666667

00:36:46.666 --> 00:36:47.850 It was much faster,

NOTE Confidence: 0.900633766666667

00:36:47.850 --> 00:36:50.370 and they had a greater drug seeking behavior,

NOTE Confidence: 0.900633766666667

00:36:50.370 --> 00:36:52.320 especially under stressful.

NOTE Confidence: 0.900633766666667

00:36:52.320 --> 00:36:53.620 Conditions similarly,

NOTE Confidence: 0.900633766666667

00:36:53.620 --> 00:36:56.410 when we gave adult animals have

NOTE Confidence: 0.900633766666667

00:36:56.410 --> 00:36:59.360 had adolescent exposure to to TFC.

NOTE Confidence: 0.900633766666667

00:36:59.360 --> 00:37:01.980 They also self administered this

NOTE Confidence: 0.900633766666667

00:37:01.980 --> 00:37:03.540 black line here that's missing.

NOTE Confidence: 0.900633766666667

00:37:03.540 --> 00:37:06.648 They also self administered more heroin.

NOTE Confidence: 0.900633766666667

00:37:06.650 --> 00:37:09.080 But when we?

NOTE Confidence: 0.900633766666667

00:37:09.080 --> 00:37:10.796 When we have our human studies,

NOTE Confidence: 0.900633766666667

00:37:10.800 --> 00:37:12.675 we're talking about cannabis and

NOTE Confidence: 0.900633766666667

00:37:12.675 --> 00:37:15.045 when we have our animal studies

NOTE Confidence: 0.900633766666667

00:37:15.045 --> 00:37:16.757 we're talking about THC.

NOTE Confidence: 0.900633766666667

00:37:16.760 --> 00:37:18.392 And we know that the cannabis

NOTE Confidence: 0.900633766666667

00:37:18.392 --> 00:37:19.480 plant is very complex,

NOTE Confidence: 0.900633766666667

00:37:19.480 --> 00:37:21.628 containing over 500 chemicals,

NOTE Confidence: 0.900633766666667

00:37:21.628 --> 00:37:25.244 many of them over 140, are cannabinoids.

NOTE Confidence: 0.900633766666667

00:37:25.244 --> 00:37:28.660 So THC yes is the primary psychoactive

NOTE Confidence: 0.900633766666667

00:37:28.660 --> 00:37:30.556 cannabinoid in cannabis plant,

NOTE Confidence: 0.900633766666667

00:37:30.556 --> 00:37:33.400 but other cannabinoids such as CBD,

NOTE Confidence: 0.900633766666667

00:37:33.400 --> 00:37:34.726 cannabidiol is.

NOTE Confidence: 0.900633766666667

00:37:34.726 --> 00:37:36.052 You know,

NOTE Confidence: 0.900633766666667

00:37:36.052 --> 00:37:39.282 also have from ecological and

NOTE Confidence: 0.900633766666667

00:37:39.282 --> 00:37:41.818 and and psychoactive properties,

NOTE Confidence: 0.900633766666667

00:37:41.820 --> 00:37:43.572 so one of the things we wanted to

NOTE Confidence: 0.900633766666667

00:37:43.572 --> 00:37:45.584 look at was that we said let's look

NOTE Confidence: 0.900633766666667

00:37:45.584 --> 00:37:47.290 at at least another cannabinoid.

NOTE Confidence: 0.900633766666667

00:37:47.290 --> 00:37:49.150 CBD, it's used to be well.

NOTE Confidence: 0.900633766666667

00:37:49.150 --> 00:37:52.054 It still technically is the second

NOTE Confidence: 0.900633766666667

00:37:52.054 --> 00:37:54.958 highest cannabinoid in the cannabis plant.

NOTE Confidence: 0.900633766666667

00:37:54.960 --> 00:37:57.067 The you know the normal cannabis plant.

NOTE Confidence: 0.900633766666667

00:37:57.070 --> 00:37:58.834 Today it's decreased dramatically

NOTE Confidence: 0.900633766666667

00:37:58.834 --> 00:38:01.039 as compared to the concentrations

NOTE Confidence: 0.900633766666667

00:38:01.039 --> 00:38:03.317 of THC that have gotten higher.

NOTE Confidence: 0.900633766666667

00:38:03.320 --> 00:38:05.770 And when we looked in our animal

NOTE Confidence: 0.900633766666667

00:38:05.770 --> 00:38:08.400 models that had been given CBD,

NOTE Confidence: 0.900633766666667

00:38:08.400 --> 00:38:09.672 we saw a different pattern to

NOTE Confidence: 0.900633766666667

00:38:09.672 --> 00:38:10.760 what we saw with THC.

NOTE Confidence: 0.900633766666667

00:38:10.760 --> 00:38:12.048 As I said earlier,

NOTE Confidence: 0.900633766666667

00:38:12.048 --> 00:38:13.658 with THC animals would invariably

NOTE Confidence: 0.900633766666667

00:38:13.658 --> 00:38:15.238 self administer more heroin is

NOTE Confidence: 0.900633766666667

00:38:15.238 --> 00:38:17.651 given to you to earlier and what we

NOTE Confidence: 0.900633766666667

00:38:17.651 --> 00:38:19.590 saw with CBD was that it decreased

NOTE Confidence: 0.900633766666667

00:38:19.590 --> 00:38:20.772 heroin seeking behavior,

NOTE Confidence: 0.900633766666667

00:38:20.772 --> 00:38:23.478 and it was very specific it

NOTE Confidence: 0.900633766666667

00:38:23.478 --> 00:38:25.358 was decreasing Q and juice.

NOTE Confidence: 0.900633766666667

00:38:25.360 --> 00:38:27.075 Currently seeking behavior so animals

NOTE Confidence: 0.900633766666667

00:38:27.075 --> 00:38:28.790 when they self administer heroin,

NOTE Confidence: 0.900633766666667

00:38:28.790 --> 00:38:30.875 just like humans,

NOTE Confidence: 0.900633766666667

00:38:30.875 --> 00:38:34.350 the environmental context becomes important.

NOTE Confidence: 0.900633766666667

00:38:34.350 --> 00:38:35.862 And for example if you showed

NOTE Confidence: 0.900633766666667

00:38:35.862 --> 00:38:36.870 them a cue or

NOTE Confidence: 0.848867088

00:38:36.931 --> 00:38:39.043 an odor when they get the drug then

NOTE Confidence: 0.848867088

00:38:39.043 --> 00:38:41.390 they will start to associate those cues.

NOTE Confidence: 0.848867088

00:38:41.390 --> 00:38:42.692 And if you only show them those

NOTE Confidence: 0.848867088

00:38:42.692 --> 00:38:43.948 cues they will press the lever.

NOTE Confidence: 0.848867088

00:38:43.950 --> 00:38:45.786 A lot of that's what we we call it.

NOTE Confidence: 0.848867088

00:38:45.790 --> 00:38:48.175 Seeking behavior and CBD was

NOTE Confidence: 0.848867088

00:38:48.175 --> 00:38:51.620 able to reduce that. So.

NOTE Confidence: 0.848867088

00:38:51.620 --> 00:38:54.040 Is CBD you know relevant?

NOTE Confidence: 0.848867088

00:38:54.040 --> 00:38:57.596 Could CBD be an A potential treatment?

NOTE Confidence: 0.848867088

00:38:57.600 --> 00:38:59.424 So as I emphasized when we look in

NOTE Confidence: 0.848867088

00:38:59.424 --> 00:39:01.108 the brains of human hearing users,

NOTE Confidence: 0.848867088

00:39:01.110 --> 00:39:03.366 we see all these changes in regard to

NOTE Confidence: 0.848867088

00:39:03.366 --> 00:39:05.118 synaptic plasticity in glutamatergic genes.

NOTE Confidence: 0.848867088

00:39:05.120 --> 00:39:07.520 We also see those in animals

NOTE Confidence: 0.848867088

00:39:07.520 --> 00:39:09.473 that self administer heroin and

NOTE Confidence: 0.848867088

00:39:09.473 --> 00:39:11.944 when we gave those animals CBD to

NOTE Confidence: 0.848867088

00:39:11.944 --> 00:39:13.639 actually reverse those changes,

NOTE Confidence: 0.848867088

00:39:13.640 --> 00:39:14.920 we could also see changes,

NOTE Confidence: 0.848867088

00:39:14.920 --> 00:39:16.660 for example with with heroin supply,

NOTE Confidence: 0.848867088

00:39:16.660 --> 00:39:18.840 administration of the cannabinoid receptor,

NOTE Confidence: 0.848867088

00:39:18.840 --> 00:39:20.740 and the cannabinoid receptor is

NOTE Confidence: 0.848867088

00:39:20.740 --> 00:39:22.260 very critical for regulating.

NOTE Confidence: 0.848867088

00:39:22.260 --> 00:39:24.860 About the transmission and

NOTE Confidence: 0.848867088

00:39:24.860 --> 00:39:27.460 CBD normalized those changes.

NOTE Confidence: 0.848867088

00:39:27.460 --> 00:39:29.504 So the question was,

NOTE Confidence: 0.848867088

00:39:29.504 --> 00:39:32.373 could it be effective in clinically?

00:39:32.373 --> 00:39:34.877 And so we ran a number of pilots

00:39:34.877 --> 00:39:36.019 here as a double.

00:39:36.020 --> 00:39:37.856 All of them were double blinded

00:39:37.856 --> 00:39:39.080 and randomized placebo controls,

00:39:39.080 --> 00:39:40.774 and those are things I think that

00:39:40.774 --> 00:39:42.268 are really critical when you're

00:39:42.268 --> 00:39:43.339 talking about cannabinoids,

00:39:43.340 --> 00:39:45.195 and especially today where everybody

00:39:45.195 --> 00:39:47.050 thinks that cannabis in general

00:39:47.111 --> 00:39:49.139 may be treatment for everything but

00:39:49.139 --> 00:39:50.955 those cannabis studies are difficult

00:39:50.955 --> 00:39:52.955 because especially if they're THC,

00:39:52.960 --> 00:39:55.120 people know when they're getting THC

00:39:55.120 --> 00:39:57.208 with CBD, it doesn't have intoxicating.

00:39:57.208 --> 00:40:00.128 Properties so at least we can have you know,

NOTE Confidence: 0.848867088

00:40:00.130 --> 00:40:01.942 good placebo control studies.

NOTE Confidence: 0.848867088

00:40:01.942 --> 00:40:05.134 So here we looked at individuals who

NOTE Confidence: 0.848867088

00:40:05.134 --> 00:40:07.899 had a heroin use disorder and when

NOTE Confidence: 0.848867088

00:40:07.899 --> 00:40:10.311 the individuals had been shown in

NOTE Confidence: 0.848867088

00:40:10.311 --> 00:40:12.633 heroin Q and then received placebo,

NOTE Confidence: 0.848867088

00:40:12.640 --> 00:40:15.316 they crave and CBD reduced that.

NOTE Confidence: 0.848867088

00:40:15.320 --> 00:40:17.315 So replicating what we saw in the

NOTE Confidence: 0.848867088

00:40:17.315 --> 00:40:19.598 animals in the in terms of their

NOTE Confidence: 0.848867088

00:40:19.598 --> 00:40:20.618 drug seeking behavior.

NOTE Confidence: 0.848867088

00:40:20.620 --> 00:40:22.528 One of the things that animals

NOTE Confidence: 0.848867088

00:40:22.528 --> 00:40:24.897 study had also showed us was that

NOTE Confidence: 0.848867088

00:40:24.897 --> 00:40:26.955 even weeks after the last CBD

NOTE Confidence: 0.848867088

00:40:26.955 --> 00:40:28.279 administration to the animals,

NOTE Confidence: 0.848867088

00:40:28.280 --> 00:40:29.915 it was still reducing their

NOTE Confidence: 0.848867088

00:40:29.915 --> 00:40:30.896 heroin seeking behavior.

NOTE Confidence: 0.848867088

00:40:30.900 --> 00:40:32.556 So when we brought people back

NOTE Confidence: 0.848867088

00:40:32.556 --> 00:40:34.606 into the lab about a week later,

NOTE Confidence: 0.848867088

00:40:34.606 --> 00:40:37.497 we could see that it was still

NOTE Confidence: 0.848867088

00:40:37.497 --> 00:40:39.608 reducing their their craving.

NOTE Confidence: 0.848867088

00:40:39.610 --> 00:40:41.116 One thing that we also saw,

NOTE Confidence: 0.848867088

00:40:41.120 --> 00:40:43.983 at least the our study participant would

NOTE Confidence: 0.848867088

00:40:43.983 --> 00:40:47.569 clear was CBD was also impacting on anxiety,

NOTE Confidence: 0.848867088

00:40:47.570 --> 00:40:49.649 so when they had gotten the heroin,

NOTE Confidence: 0.848867088

00:40:49.650 --> 00:40:52.146 Hugh and and been given placebo,

NOTE Confidence: 0.848867088

00:40:52.150 --> 00:40:53.974 they they were anxious and when

NOTE Confidence: 0.848867088

00:40:53.974 --> 00:40:56.368 they got to CBD it reduced the

NOTE Confidence: 0.848867088

00:40:56.368 --> 00:40:58.223 anxiety that cue induced again.

NOTE Confidence: 0.848867088

00:40:58.230 --> 00:41:01.219 Cue induced angularity and a week later

NOTE Confidence: 0.848867088

00:41:01.219 --> 00:41:03.610 it's still reduced their anxiety.

NOTE Confidence: 0.848867088

00:41:03.610 --> 00:41:05.020 We hadn't studied anxiety in

NOTE Confidence: 0.848867088

00:41:05.020 --> 00:41:05.866 our animal models,

00:41:05.870 --> 00:41:07.678 but we did try to look at other

00:41:07.678 --> 00:41:10.470 aspects of in terms of, you know,

00:41:10.470 --> 00:41:13.046 in our human studies in not just the

00:41:13.046 --> 00:41:15.270 self reports of craving and anxiety,

00:41:15.270 --> 00:41:16.550 but also these physiological

00:41:16.550 --> 00:41:17.510 measures of stress.

00:41:17.510 --> 00:41:19.334 For example, cortisol levels.

00:41:19.334 --> 00:41:22.505 So when when people had been given

00:41:22.505 --> 00:41:25.550 the drug queue and had gotten placebo,

00:41:25.550 --> 00:41:27.550 their cortisol levels went up

00:41:27.550 --> 00:41:29.150 and CBD reduced that.

00:41:29.150 --> 00:41:29.566 Similarly,

00:41:29.566 --> 00:41:32.894 their heart rate went up when given the

00:41:32.894 --> 00:41:36.256 drug queue and placebo and CBE reduce that.

00:41:36.260 --> 00:41:37.148 As I said,

00:41:37.148 --> 00:41:39.220 we hadn't really looked at anxiety in

NOTE Confidence: 0.789302832307692

00:41:39.288 --> 00:41:41.316 our animal models, but based on what

NOTE Confidence: 0.789302832307692

00:41:41.316 --> 00:41:43.420 we we were we saw in our humans,

NOTE Confidence: 0.789302832307692

00:41:43.420 --> 00:41:45.620 we've now gone back to look at that

NOTE Confidence: 0.789302832307692

00:41:45.620 --> 00:41:48.080 and to also try to understand what's

NOTE Confidence: 0.789302832307692

00:41:48.080 --> 00:41:50.291 the mechanism of action by which

NOTE Confidence: 0.789302832307692

00:41:50.291 --> 00:41:52.972 CD may be working here in my post

NOTE Confidence: 0.789302832307692

00:41:52.972 --> 00:41:55.415 that Jackie Ferlin we looked at,

NOTE Confidence: 0.789302832307692

00:41:55.415 --> 00:41:58.169 we tried to induce anxiety in our

NOTE Confidence: 0.789302832307692

00:41:58.169 --> 00:42:00.430 animals plastic with in terms of shocking

NOTE Confidence: 0.789302832307692

00:42:00.492 --> 00:42:02.858 animals and when the animals are shocked,

NOTE Confidence: 0.789302832307692

00:42:02.860 --> 00:42:03.924 they're given a queue.

NOTE Confidence: 0.789302832307692

00:42:03.924 --> 00:42:05.859 Here we give them this lemon odor

NOTE Confidence: 0.789302832307692

00:42:05.859 --> 00:42:07.557 and then we assess their anxiety.

NOTE Confidence: 0.789302832307692

00:42:07.560 --> 00:42:08.736 Related behavior here.

NOTE Confidence: 0.789302832307692

00:42:08.736 --> 00:42:11.480 This is using the light dark spots

00:42:11.552 --> 00:42:13.862 and we could see that in those

00:42:13.862 --> 00:42:16.074 animals that when they've been given

00:42:16.074 --> 00:42:18.350 vehicle and they had were exposed

00:42:18.350 --> 00:42:21.825 to the lemon queue and they showed

00:42:21.825 --> 00:42:24.485 increased anxiety related behavior.

00:42:24.490 --> 00:42:27.850 But given CBD CBD completely reduced,

00:42:27.850 --> 00:42:30.790 that Q induced limit.

00:42:30.790 --> 00:42:31.730 Behavioral response.

00:42:31.730 --> 00:42:34.080 We're now, as I said,

00:42:34.080 --> 00:42:35.610 trying to understand how CBD

00:42:35.610 --> 00:42:37.140 might be having its effects,

00:42:37.140 --> 00:42:40.896 so that we can perhaps identify

00:42:40.896 --> 00:42:43.841 even non CBD related development.

00:42:43.841 --> 00:42:46.487 Non CBD related medications based on

00:42:46.487 --> 00:42:49.238 the the biology of what's happening.

00:42:49.240 --> 00:42:51.336 Not going to tell you some of the

00:42:51.340 --> 00:42:53.938 the specific mechanisms that we see,

00:42:53.940 --> 00:42:56.164 but one of the things that's clear is

00:42:56.164 --> 00:42:58.239 that there are disturbances in these

00:42:58.240 --> 00:43:00.298 circuits related to the nucleus accumbens.

00:43:00.300 --> 00:43:02.930 The basolateral amygdala and prelimbic.

00:43:02.930 --> 00:43:04.574 Facts, not surprisingly,

00:43:04.574 --> 00:43:05.670 but interestingly,

00:43:05.670 --> 00:43:06.680 if we just, for example,

00:43:06.680 --> 00:43:07.672 within the nucleus accumbens,

00:43:07.672 --> 00:43:08.912 here is just a shell.

00:43:08.920 --> 00:43:10.621 We can see that there is a

00:43:10.621 --> 00:43:11.989 significant changes where some genes

00:43:11.989 --> 00:43:13.459 are downregulated in other genes,

00:43:13.460 --> 00:43:15.790 upregulated when in animals when

00:43:15.790 --> 00:43:18.120 they're exposed again to this,

00:43:18.120 --> 00:43:20.160 this queuing juice stressor and

00:43:20.160 --> 00:43:22.200 they show this anxiety behavior,

00:43:22.200 --> 00:43:24.279 and when you look at the animals

00:43:24.279 --> 00:43:26.478 that had gotten CBD and their

00:43:26.478 --> 00:43:27.717 behaviors were normalized.

00:43:27.720 --> 00:43:30.198 It's just it shows that CBD

00:43:30.198 --> 00:43:32.426 reverses or even eliminates these

00:43:32.426 --> 00:43:34.926 particular genes that are changed.

00:43:34.930 --> 00:43:37.920 So. Does cannabidiol hold promise?

00:43:37.920 --> 00:43:39.051 At least here,

00:43:39.051 --> 00:43:41.325 we've been able to do clinical trials.

00:43:41.325 --> 00:43:42.855 We're still working on one of

00:43:42.855 --> 00:43:43.939 the effective doses,

00:43:43.940 --> 00:43:45.460 and the formulations and

00:43:45.460 --> 00:43:46.600 the delivery systems,

00:43:46.600 --> 00:43:50.219 but similar to what we you know

00:43:50.220 --> 00:43:52.922 I mentioned in terms of the other

00:43:52.922 --> 00:43:55.529 strategies that we're looking at in

00:43:55.529 --> 00:43:57.343 translating to developing potential

00:43:57.343 --> 00:43:59.558 medications for opiate use disorder.

00:43:59.560 --> 00:44:03.052 It may not be specific CBD for just opioids.

00:44:03.060 --> 00:44:04.284 Other groups have shown,

00:44:04.284 --> 00:44:06.256 for example, with alcohol again.

00:44:06.256 --> 00:44:08.516 And here weeks after their

00:44:08.516 --> 00:44:10.650 last alcohol intake animals,

00:44:10.650 --> 00:44:13.060 CBD still reduce their alcohol

00:44:13.060 --> 00:44:14.024 seeking behavior.

00:44:14.030 --> 00:44:16.641 And even when they're the stress induced

00:44:16.641 --> 00:44:18.718 against here, it's just a shock.

00:44:18.718 --> 00:44:19.050 Again.

00:44:19.050 --> 00:44:21.521 You can also see that CBD still

NOTE Confidence: 0.789302832307692

00:44:21.521 --> 00:44:23.810 reduce their alcohol seeking behavior.

NOTE Confidence: 0.789302832307692

00:44:23.810 --> 00:44:27.456 But there may be some things that would sex.

NOTE Confidence: 0.789302832307692

00:44:27.456 --> 00:44:28.362 For example,

NOTE Confidence: 0.789302832307692

00:44:28.362 --> 00:44:31.080 a group looking at binge drinking

NOTE Confidence: 0.789302832307692

00:44:31.159 --> 00:44:33.882 in in the mouse model found that

NOTE Confidence: 0.789302832307692

00:44:33.882 --> 00:44:36.096 although CBD did reduce alcohol

NOTE Confidence: 0.789302832307692

00:44:36.096 --> 00:44:38.378 intake in the mail animals,

NOTE Confidence: 0.789302832307692

00:44:38.378 --> 00:44:41.420 it did not do that in the female until

NOTE Confidence: 0.789302832307692

00:44:41.492 --> 00:44:44.045 they increased the dose of CBD significantly.

NOTE Confidence: 0.789302832307692

00:44:44.045 --> 00:44:47.205 So there's still a lot that we have

NOTE Confidence: 0.789302832307692

00:44:47.205 --> 00:44:49.682 to learn and doses are important,

NOTE Confidence: 0.789302832307692

00:44:49.682 --> 00:44:52.627 but at least now we're able to

NOTE Confidence: 0.789302832307692

00:44:52.627 --> 00:44:54.717 expand our our small studies.

NOTE Confidence: 0.767624137117647

00:44:54.720 --> 00:44:57.750 And now we're also looking at in terms of a

NOTE Confidence: 0.767624137117647

00:44:57.820 --> 00:45:00.774 big clinical trial with CANNABIDOL to see.

NOTE Confidence: 0.767624137117647

00:45:00.780 --> 00:45:03.060 Indeed again, you know, placebo,

NOTE Confidence: 0.767624137117647

00:45:03.060 --> 00:45:04.179 randomized placebo control,

NOTE Confidence: 0.767624137117647

00:45:04.179 --> 00:45:06.790 and to see also doing your imaging

NOTE Confidence: 0.767624137117647

00:45:06.855 --> 00:45:09.023 studies to see if we can start in

NOTE Confidence: 0.767624137117647

00:45:09.023 --> 00:45:11.046 humans like our animal models to

NOTE Confidence: 0.767624137117647

00:45:11.046 --> 00:45:12.821 understand what are the neural

NOTE Confidence: 0.767624137117647

00:45:12.821 --> 00:45:15.750 systems that are changed with CBD.

NOTE Confidence: 0.767624137117647

00:45:15.750 --> 00:45:21.110 So clearly in looking at the human brain,

NOTE Confidence: 0.767624137117647

00:45:21.110 --> 00:45:23.648 it has taught us a lot that you know,

NOTE Confidence: 0.767624137117647

00:45:23.650 --> 00:45:25.680 although initially we have focused

NOTE Confidence: 0.767624137117647

00:45:25.680 --> 00:45:28.566 on dopamine and and even the opioid

NOTE Confidence: 0.767624137117647

00:45:28.566 --> 00:45:30.792 system in targeting for medication,

NOTE Confidence: 0.767624137117647

00:45:30.792 --> 00:45:34.102 but it's about epigenetics and

NOTE Confidence: 0.767624137117647

00:45:34.102 --> 00:45:37.359 synaptic plasticity and these to

NOTE Confidence: 0.767624137117647

00:45:37.359 --> 00:45:41.217 me and also those those neural.

NOTE Confidence: 0.767624137117647

00:45:41.220 --> 00:45:44.016 Networks and those systems that really

NOTE Confidence: 0.767624137117647

00:45:44.016 --> 00:45:46.867 relate as well to cognition in part,

NOTE Confidence: 0.767624137117647

00:45:46.867 --> 00:45:48.841 and those are things that we're

NOTE Confidence: 0.767624137117647

00:45:48.841 --> 00:45:50.200 definitely trying to develop,

NOTE Confidence: 0.767624137117647

00:45:50.200 --> 00:45:52.220 and the important thing about

NOTE Confidence: 0.767624137117647

00:45:52.220 --> 00:45:54.240 all of these epigenetic changes

NOTE Confidence: 0.767624137117647

00:45:54.313 --> 00:45:56.168 is that they are reversible.

NOTE Confidence: 0.767624137117647

00:45:56.170 --> 00:45:57.078 So yes,

NOTE Confidence: 0.767624137117647

00:45:57.078 --> 00:45:59.348 the epigenetic mechanisms maintain these

NOTE Confidence: 0.767624137117647

00:45:59.348 --> 00:46:01.620 long term sensitivity of the brain,

NOTE Confidence: 0.767624137117647

00:46:01.620 --> 00:46:03.314 but it's because we really haven't found

NOTE Confidence: 0.767624137117647

00:46:03.314 --> 00:46:04.759 the right targets to reverse them,

NOTE Confidence: 0.767624137117647

00:46:04.760 --> 00:46:07.418 because these tags are like genetics,

NOTE Confidence: 0.767624137117647

00:46:07.420 --> 00:46:08.056 are reversible.

NOTE Confidence: 0.767624137117647

00:46:08.056 --> 00:46:11.150 So I had mentioned a lot of the people.

NOTE Confidence: 0.767624137117647

00:46:11.150 --> 00:46:12.370 Who had you know,

NOTE Confidence: 0.767624137117647

00:46:12.370 --> 00:46:14.200 contributed to a lot of the

NOTE Confidence: 0.767624137117647

00:46:14.275 --> 00:46:15.767 work that we're doing?

NOTE Confidence: 0.767624137117647

00:46:15.770 --> 00:46:17.717 I didn't show like Alex **** where

NOTE Confidence: 0.767624137117647

00:46:17.717 --> 00:46:20.706 working on CBD and or heroin users,

NOTE Confidence: 0.767624137117647

00:46:20.710 --> 00:46:22.462 and a lot of our clinical

NOTE Confidence: 0.767624137117647

00:46:22.462 --> 00:46:23.630 team and Karen backing,

NOTE Confidence: 0.767624137117647

00:46:23.630 --> 00:46:26.157 and in large part in running the

NOTE Confidence: 0.767624137117647

00:46:26.157 --> 00:46:28.363 operations of our clinical trials

NOTE Confidence: 0.767624137117647

00:46:28.363 --> 00:46:31.201 and doctor and soul systems of

NOTE Confidence: 0.767624137117647

00:46:31.201 --> 00:46:33.370 Amazing Addiction medicine physician

NOTE Confidence: 0.767624137117647

00:46:33.370 --> 00:46:35.026 who's been great to work with.

NOTE Confidence: 0.767624137117647

00:46:35.030 --> 00:46:36.955 So with that I will take any

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00:46:36.955 --> 00:46:38.489 questions that you might have.

NOTE Confidence: 0.767624137117647

00:46:38.490 --> 00:46:40.000 Thank you.