WEBVTT

NOTE duration:"00:46:40"

NOTE recognizability:0.867

NOTE language:en-us

NOTE Confidence: 0.847070010952381

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

NOTE Confidence: 0.847070010952381

 $00:00:05.841 \rightarrow 00:00:07.648$ really great introduction and I'm let

NOTE Confidence: 0.847070010952381

 $00{:}00{:}07{.}648 \dashrightarrow 00{:}00{:}09{.}610$ me share my screen and I do that.

NOTE Confidence: 0.847070010952381

 $00{:}00{:}09{.}610 \dashrightarrow 00{:}00{:}13{.}508$ You know, it's it's quite an honor to

NOTE Confidence: 0.847070010952381

 $00:00:13.508 \dashrightarrow 00:00:17.834$ be given this opportunity to be the.

NOTE Confidence: 0.847070010952381

 $00:00:17.840 \rightarrow 00:00:20.759$ Ribicoff speaker for for this year and

NOTE Confidence: 0.847070010952381

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

NOTE Confidence: 0.847070010952381

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

NOTE Confidence: 0.847070010952381

 $00:00:26.636 \longrightarrow 00:00:27.620$ And obviously everybody.

NOTE Confidence: 0.847070010952381

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

NOTE Confidence: 0.847070010952381

 $00{:}00{:}30{.}385 \dashrightarrow 00{:}00{:}32{.}464$ of understanding the importance of

NOTE Confidence: 0.847070010952381

 $00{:}00{:}32{.}464 \dashrightarrow 00{:}00{:}34{.}918$ evidence based medicine and the only

NOTE Confidence: 0.847070010952381

 $00{:}00{:}34{.}918 \dashrightarrow 00{:}00{:}37{.}578$ 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

 $00:00:39.414 \rightarrow 00:00:41.388$ this close interaction between basic

NOTE Confidence: 0.847070010952381

 $00{:}00{:}41.388 \dashrightarrow 00{:}00{:}43.398$ scientists and clinical and the

NOTE Confidence: 0.847070010952381

 $00:00:43.398 \longrightarrow 00:00:45.540$ and the clinical and clinicians.

NOTE Confidence: 0.847070010952381

 $00:00:45.540 \longrightarrow 00:00:48.666$ 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

 $00:00:52.598 \rightarrow 00:00:54.775$ pictures of everyone and the first

NOTE Confidence: 0.847070010952381

 $00{:}00{:}54.775 \dashrightarrow 00{:}00{:}57.639$ 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

 $00{:}00{:}59{.}841 \dashrightarrow 00{:}01{:}02{.}646$ in terms of the the work that I'll

NOTE Confidence: 0.847070010952381

 $00:01:02.646 \longrightarrow 00:01:04.881$ be talking to you about today.

NOTE Confidence: 0.847070010952381

 $00:01:04.881 \rightarrow 00:01:07.323$ And basically you know for me,

NOTE Confidence: 0.847070010952381

 $00{:}01{:}07{.}330 \dashrightarrow 00{:}01{:}09{.}460$ the Addiction Institute of Mount

NOTE Confidence: 0.847070010952381

 $00:01:09.460 \longrightarrow 00:01:12.858$ Sinai that I direct is.

NOTE Confidence: 0.847070010952381

 $00:01:12.860 \rightarrow 00:01:15.422$ It brought home the critical nature of

NOTE Confidence: 0.847070010952381

 $00:01:15.422 \rightarrow 00:01:18.176$ of of research and where we are today,

- NOTE Confidence: 0.847070010952381
- $00:01:18.180 \longrightarrow 00:01:20.595$ 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
- $00:01:24.820 \longrightarrow 00:01:26.560$ we treat over 6000 people with
- NOTE Confidence: 0.847070010952381
- $00{:}01{:}26.560 \dashrightarrow 00{:}01{:}27.720$ an opiate use disorder.
- NOTE Confidence: 0.847070010952381
- $00{:}01{:}27.720 \dashrightarrow 00{:}01{:}29.953$ So you can imagine the the challenges
- NOTE Confidence: 0.847070010952381
- $00:01:29.953 \longrightarrow 00:01:32.035$ there and it really reflects the
- NOTE Confidence: 0.847070010952381
- $00:01:32.035 \longrightarrow 00:01:34.492$ opioid crisis that we are still in.
- NOTE Confidence: 0.847070010952381
- $00:01:34.500 \longrightarrow 00:01:35.748$ And as many of you know,
- NOTE Confidence: 0.847070010952381
- $00{:}01{:}35{.}750 \dashrightarrow 00{:}01{:}37{.}925$ you know the economic burden
- NOTE Confidence: 0.847070010952381
- $00:01:37.925 \longrightarrow 00:01:39.845$ of the opioid crisis.
- NOTE Confidence: 0.847070010952381
- $00:01:39.845 \longrightarrow 00:01:41.825$ The healthcare system under
- NOTE Confidence: 0.847070010952381
- $00:01:41.825 \rightarrow 00:01:43.310$ 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
- $00{:}01{:}44.510 \dashrightarrow 00{:}01{:}46.827$ is it's costing nearly three times more
- NOTE Confidence: 0.847070010952381

 $00:01:46.827 \rightarrow 00:01:48.970$ than other medical disorders to trade,

NOTE Confidence: 0.847070010952381

 $00{:}01{:}48{.}970 \dashrightarrow 00{:}01{:}50{.}752$ and the treatments that are that

NOTE Confidence: 0.847070010952381

 $00:01:50.752 \rightarrow 00:01:52.469$ are available are often not used,

NOTE Confidence: 0.847070010952381

 $00{:}01{:}52.470 \dashrightarrow 00{:}01{:}55.868$ and some of them not suitable and we

NOTE Confidence: 0.847070010952381

 $00:01:55.868 \dashrightarrow 00:01:58.622$ still have so many overdose deaths

NOTE Confidence: 0.847070010952381

 $00{:}01{:}58.622 \dashrightarrow 00{:}02{:}01.901$ today and that has been the crisis

NOTE Confidence: 0.847070010952381

 $00:02:01.901 \dashrightarrow 00:02:04.486$ have been exacerbated by covid's.

NOTE Confidence: 0.847070010952381

 $00:02:04.490 \rightarrow 00:02:06.530$ COVID has exacerbated so many things,

NOTE Confidence: 0.847070010952381

 $00{:}02{:}06{.}530 \dashrightarrow 00{:}02{:}08{.}594$ but the stress and social isolation

NOTE Confidence: 0.847070010952381

 $00:02:08.594 \longrightarrow 00:02:09.970$ has increased drug use.

NOTE Confidence: 0.847070010952381

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

NOTE Confidence: 0.847070010952381

 $00{:}02{:}10.660 \dashrightarrow 00{:}02{:}12.270$ you see that a lot with opioids,

NOTE Confidence: 0.847070010952381

 $00:02:12.270 \longrightarrow 00:02:14.160$ and especially unfortunately.

NOTE Confidence: 0.847070010952381

 $00:02:14.160 \longrightarrow 00:02:15.420$ With fentanyl,

NOTE Confidence: 0.847070010952381

 $00:02:15.420 \longrightarrow 00:02:18.624$ that 4th wave of opioids that

NOTE Confidence: 0.847070010952381

 $00:02:18.624 \rightarrow 00:02:21.300$ contribute significantly to to dread

 $00:02:21.300 \rightarrow 00:02:23.900$ to drug overdose and so that you know.

NOTE Confidence: 0.847070010952381

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

NOTE Confidence: 0.847070010952381

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

NOTE Confidence: 0.847070010952381

 $00:02:29.240 \longrightarrow 00:02:30.500$ so you know.

NOTE Confidence: 0.847070010952381

 $00:02:30.500 \rightarrow 00:02:33.020$ So for me, the question has always been,

NOTE Confidence: 0.847070010952381

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

NOTE Confidence: 0.847070010952381

 $00:02:35.180 \longrightarrow 00:02:37.007$ What's what we're doing and a part

NOTE Confidence: 0.847070010952381

 $00:02:37.007 \dashrightarrow 00:02:38.878$ of that comes back to treatments.

NOTE Confidence: 0.847070010952381

 $00{:}02{:}38.880 \dashrightarrow 00{:}02{:}40.668$ And when you look at treatments

NOTE Confidence: 0.847070010952381

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

NOTE Confidence: 0.847070010952381

 $00:02:41.860 \rightarrow 00:02:44.348$ you know there is actually a long history.

NOTE Confidence: 0.847070010952381

 $00{:}02{:}44.350 \dashrightarrow 00{:}02{:}47.008$ And it's interesting that there were

NOTE Confidence: 0.847070010952381

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

NOTE Confidence: 0.847070010952381

 $00{:}02{:}49{.}275 \dashrightarrow 00{:}02{:}52{.}020$ and as you look across the years of the

NOTE Confidence: 0.847070010952381

 $00{:}02{:}52.096 \dashrightarrow 00{:}02{:}54.606$ medications that have been developed.

 $00:02:54.610 \longrightarrow 00:02:55.702$ There've been a number.

NOTE Confidence: 0.847070010952381

 $00{:}02{:}55{.}702 \dashrightarrow 00{:}02{:}57{.}722$ I'm going to focus on the opioids

NOTE Confidence: 0.847070010952381

 $00{:}02{:}57.722 \dashrightarrow 00{:}02{:}59.630$ because most of the the treatments

NOTE Confidence: 0.847070010952381

 $00:02:59.630 \rightarrow 00:03:01.608$ that have been developed and hear

NOTE Confidence: 0.847070010952381

 $00:03:01.608 \longrightarrow 00:03:04.530$ from 1964 with methadone to today.

NOTE Confidence: 0.847070010952381

 $00:03:04.530 \rightarrow 00:03:07.946$ 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

 $00:03:11.290 \rightarrow 00:03:12.978$ not only methadone, buprenorphine,

NOTE Confidence: 0.847070010952381

 $00:03:12.978 \longrightarrow 00:03:14.244$ and of course,

NOTE Confidence: 0.883464144

 $00:03:14.250 \rightarrow 00:03:16.410$ we have naltrexone,

NOTE Confidence: 0.883464144

 $00:03:16.410 \rightarrow 00:03:19.998$ especially for trying to reduce overdose.

NOTE Confidence: 0.883464144

 $00:03:19.998 \longrightarrow 00:03:22.342$ And there are, of course

NOTE Confidence: 0.883464144

 $00:03:22.342 \longrightarrow 00:03:23.806$ behavioral therapies as well,

NOTE Confidence: 0.883464144

 $00:03:23.810 \rightarrow 00:03:25.680$ but as I mentioned earlier,

NOTE Confidence: 0.883464144

 $00{:}03{:}25{.}680 \dashrightarrow 00{:}03{:}27{.}432$ the problem that we have with a lot

NOTE Confidence: 0.883464144

 $00:03:27.432 \rightarrow 00:03:29.361$ of the treatments is that only about

- NOTE Confidence: 0.883464144
- $00:03:29.361 \longrightarrow 00:03:31.540 \ 20\%$ of the people who need opioid
- NOTE Confidence: 0.883464144
- $00:03:31.540 \longrightarrow 00:03:33.020$ use treatment actually receive it,
- NOTE Confidence: 0.883464144
- $00{:}03{:}33{.}020 \dashrightarrow 00{:}03{:}35{.}420$ and the the reasons are numerous
- NOTE Confidence: 0.883464144
- $00:03:35.420 \rightarrow 00:03:37.899$ things start with even the stigma,
- NOTE Confidence: 0.883464144
- 00:03:37.900 --> 00:03:38.686 because unfortunately,
- NOTE Confidence: 0.883464144
- $00:03:38.686 \rightarrow 00:03:41.044$ 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
- $00:03:43.160 \longrightarrow 00:03:46.640$ The stigma associated with with opioid
- NOTE Confidence: 0.883464144
- $00{:}03{:}46{.}640 \dashrightarrow 00{:}03{:}49{.}214$ agonist and many programs not wanting
- NOTE Confidence: 0.883464144
- $00:03:49.214 \longrightarrow 00:03:52.123$ to quote UN quote their their their
- NOTE Confidence: 0.883464144
- $00:03:52.123 \rightarrow 00:03:54.384$ clients to be on any medication.
- NOTE Confidence: 0.883464144
- $00:03:54.384 \longrightarrow 00:03:56.808$ That might be have an addictive
- NOTE Confidence: 0.883464144
- $00:03:56.808 \rightarrow 00:03:57.616$ potential itself,
- NOTE Confidence: 0.883464144
- $00{:}03{:}57{.}620 \dashrightarrow 00{:}03{:}59{.}538$ so there are these challenges as well.
- NOTE Confidence: 0.883464144
- $00:03:59.540 \rightarrow 00:04:00.820$ And ironically,
- NOTE Confidence: 0.883464144

 $00:04:00.820 \rightarrow 00:04:02.740$ the governmental regulations

NOTE Confidence: 0.883464144

 $00:04:02.740 \longrightarrow 00:04:05.300$ of using these opioid.

NOTE Confidence: 0.883464144

 $00:04:05.300 \rightarrow 00:04:07.540$ Treatments make it very challenging,

NOTE Confidence: 0.883464144

 $00:04:07.540 \longrightarrow 00:04:09.225$ clinically and for patients to

NOTE Confidence: 0.883464144

 $00{:}04{:}09{.}225 \dashrightarrow 00{:}04{:}10{.}573$ even access these treatments,

NOTE Confidence: 0.883464144

 $00:04:10.580 \longrightarrow 00:04:12.548$ sometimes in places in the US

NOTE Confidence: 0.883464144

 $00:04:12.548 \longrightarrow 00:04:14.674$ where people have to drive or find

NOTE Confidence: 0.883464144

 $00:04:14.674 \longrightarrow 00:04:16.880$ 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

 $00:04:20.280 \rightarrow 00:04:22.856$ we really have had this one size fit

NOTE Confidence: 0.883464144

 $00{:}04{:}22.856 \dashrightarrow 00{:}04{:}25.678$ all approach to treating opiate use disorder.

NOTE Confidence: 0.883464144

 $00:04:25.680 \longrightarrow 00:04:27.731$ So for me, when you look at

NOTE Confidence: 0.883464144

 $00:04:27.731 \longrightarrow 00:04:29.300$ the neurobiology of addiction,

NOTE Confidence: 0.883464144

 $00:04:29.300 \longrightarrow 00:04:31.004$ you know the question is what

NOTE Confidence: 0.883464144

 $00:04:31.004 \longrightarrow 00:04:31.856$ have we learned?

NOTE Confidence: 0.883464144

 $00:04:31.860 \rightarrow 00:04:34.100$ We have learned a lot really a lot.

- NOTE Confidence: 0.883464144
- $00:04:34.100 \longrightarrow 00:04:35.570$ We have learned a lot about.

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

NOTE Confidence: 0.883464144

 $00:04:37.778 \longrightarrow 00:04:39.986$ neural circuits relevant to

NOTE Confidence: 0.883464144

 $00:04:39.990 \rightarrow 00:04:42.002$ phenotypes important for addiction.

NOTE Confidence: 0.883464144

 $00{:}04{:}42.002 \dashrightarrow 00{:}04{:}43.008$ For example,

NOTE Confidence: 0.883464144

 $00{:}04{:}43.010 \dashrightarrow 00{:}04{:}45.117$ the ventral steroidal area that which is

NOTE Confidence: 0.883464144

 $00:04:45.117 \rightarrow 00:04:47.128$ a nucleus accumbens important for reward,

NOTE Confidence: 0.883464144

 $00:04:47.130 \longrightarrow 00:04:49.426$ expectation, goal directed behavior.

NOTE Confidence: 0.883464144

 $00{:}04{:}49{.}426 \dashrightarrow 00{:}04{:}51{.}148$ The dorsal striatum.

NOTE Confidence: 0.883464144

 $00:04:51.150 \rightarrow 00:04:54.130$ Important for habit, habitual formation,

NOTE Confidence: 0.883464144

 $00:04:54.130 \longrightarrow 00:04:55.180$ the prefrontal cortex,

NOTE Confidence: 0.883464144

 $00{:}04{:}55{.}180 \dashrightarrow 00{:}04{:}57{.}923$ and the number of the it's sub regions

NOTE Confidence: 0.883464144

 $00{:}04{:}57{.}923 \dashrightarrow 00{:}05{:}00{.}426$ 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.

 $00:05:05.810 \rightarrow 00:05:08.130$ Emotional regulation and so on.

NOTE Confidence: 0.883464144

 $00{:}05{:}08{.}130 \dashrightarrow 00{:}05{:}10{.}934$ And we do know that for the most

NOTE Confidence: 0.883464144

 $00{:}05{:}10{.}934 \dashrightarrow 00{:}05{:}13{.}090$ drugs of abuse that the use acute

NOTE Confidence: 0.883464144

 $00:05:13.158 \longrightarrow 00:05:15.097$ use of the drug does lead to,

NOTE Confidence: 0.883464144

 $00:05:15.100 \longrightarrow 00:05:15.998$ for example,

NOTE Confidence: 0.883464144

 $00:05:15.998 \rightarrow 00:05:17.794$ this increasing dopamine that's

NOTE Confidence: 0.883464144

 $00{:}05{:}17.794 \dashrightarrow 00{:}05{:}21.210$ associated with business phoria and

NOTE Confidence: 0.883464144

 $00:05:21.210 \longrightarrow 00:05:24.066$ so many research has gone into this.

NOTE Confidence: 0.883464144

 $00{:}05{:}24.070 \dashrightarrow 00{:}05{:}27.830$ This acute changes that occurs with drug use.

NOTE Confidence: 0.883464144

 $00:05:27.830 \longrightarrow 00:05:28.619$ So for me,

NOTE Confidence: 0.883464144

 $00:05:28.619 \rightarrow 00:05:30.460$ a quick question that I asked many

NOTE Confidence: 0.883464144

 $00{:}05{:}30{.}519 \dashrightarrow 00{:}05{:}32{.}682$ many years ago that then became the

NOTE Confidence: 0.883464144

 $00:05:32.682 \rightarrow 00:05:34.657$ foundation for my research was really

NOTE Confidence: 0.883464144

 $00:05:34.657 \rightarrow 00:05:37.322$ what have we learned about the human brain,

NOTE Confidence: 0.883464144

 $00:05:37.322 \dashrightarrow 00:05:38.810$ especially the molecular level.

NOTE Confidence: 0.883464144

 $00:05:38.810 \longrightarrow 00:05:40.675$ Because it was so challenging

- NOTE Confidence: 0.883464144
- $00:05:40.675 \longrightarrow 00:05:43.310$ to get that kind of insights.

- 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
- $00:05:45.110 \longrightarrow 00:05:46.678$ let's start studying the
- NOTE Confidence: 0.883464144

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

NOTE Confidence: 0.883464144

 $00:05:47.860 \dashrightarrow 00:05:51.227$ 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

 $00:05:52.688 \rightarrow 00:05:55.167$ we know that you know studying

NOTE Confidence: 0.883464144

 $00:05:55.167 \longrightarrow 00:05:56.862$ 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
- $00:05:58.390 \rightarrow 00:06:00.688$ and I'll come back to epigenetic
- NOTE Confidence: 0.883464144
- $00{:}06{:}00{.}688 \dashrightarrow 00{:}06{:}02{.}656$ mechanisms that Marina mentioned that

NOTE Confidence: 0.883464144

 $00{:}06{:}02.656 \dashrightarrow 00{:}06{:}04.511$ altogether this leads to changing

NOTE Confidence: 0.883464144

 $00{:}06{:}04{.}511 \dashrightarrow 00{:}06{:}06{.}680$ proteins in the function and the

NOTE Confidence: 0.883464144

 $00:06:06.680 \dashrightarrow 00:06:08.860$ phenotype of events of the disease so.

 $00{:}06{:}08{.}860 \dashrightarrow 00{:}06{:}11{.}100$ That's where I'm going to start and

NOTE Confidence: 0.883464144

 $00{:}06{:}11{.}100 \dashrightarrow 00{:}06{:}13{.}294$ 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

 $00:06:14.986 \longrightarrow 00:06:17.200$ 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

 $00:06:18.927 \longrightarrow 00:06:20.452$ brain that guides our animal

NOTE Confidence: 0.883464144

 $00{:}06{:}20{.}452 \dashrightarrow 00{:}06{:}23{.}205$ 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

 $00{:}06{:}24.310 \dashrightarrow 00{:}06{:}26.325$ So when we looked for

NOTE Confidence: 0.883464144

 $00:06:26.325 \rightarrow 00:06:28.340$ example here in the striatum

NOTE Confidence: 0.822189974285714

 $00{:}06{:}28.425 \dashrightarrow 00{:}06{:}30.197$ of human heroin users.

NOTE Confidence: 0.822189974285714

 $00:06:30.200 \longrightarrow 00:06:34.830$ Using approaches that were agnostic,

NOTE Confidence: 0.822189974285714

 $00{:}06{:}34.830 \dashrightarrow 00{:}06{:}38.100$ Welsh and unbiased in a way of

NOTE Confidence: 0.822189974285714

 $00:06:38.100 \longrightarrow 00:06:39.520$ looking at thousands of genes,

NOTE Confidence: 0.822189974285714

 $00:06:39.520 \rightarrow 00:06:42.085$ whether it initially was microarray

NOTE Confidence: 0.822189974285714

 $00:06:42.085 \rightarrow 00:06:44.650$ strategies or more recently RNA

 $00:06:44.729 \dashrightarrow 00:06:47.177$ sequencing of the transcriptome,

NOTE Confidence: 0.822189974285714

 $00:06:47.180 \longrightarrow 00:06:50.491$ we could see clearly that the gene

NOTE Confidence: 0.822189974285714

 $00:06:50.491 \rightarrow 00:06:52.462$ expression signature inhering users

NOTE Confidence: 0.822189974285714

 $00{:}06{:}52.462 \dashrightarrow 00{:}06{:}54.966$ differed from normal controls and

NOTE Confidence: 0.822189974285714

 $00{:}06{:}54.966 \dashrightarrow 00{:}06{:}57.576$ where it differed was interesting

NOTE Confidence: 0.822189974285714

 $00{:}06{:}57{.}576 \dashrightarrow 00{:}07{:}00{.}100$ because we saw much greater.

NOTE Confidence: 0.822189974285714

 $00:07:00.100 \rightarrow 00:07:02.570$ This regulation of glutamatergic genes

NOTE Confidence: 0.822189974285714

 $00:07:02.570 \longrightarrow 00:07:05.583$ and perhaps not really surprising of

NOTE Confidence: 0.822189974285714

 $00:07:05.583 \rightarrow 00:07:07.928$ the synaptic plasticity related genes.

NOTE Confidence: 0.822189974285714

 $00:07:07.930 \rightarrow 00:07:10.390$ This the striatum receives really

NOTE Confidence: 0.822189974285714

 $00:07:10.390 \longrightarrow 00:07:12.850$ strong innovations from the prefrontal

NOTE Confidence: 0.822189974285714

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

NOTE Confidence: 0.822189974285714

 $00:07:15.664 \dashrightarrow 00:07:17.719$ animal studies that that is really

NOTE Confidence: 0.822189974285714

 $00{:}07{:}17.720 \dashrightarrow 00{:}07{:}19.604$ critical for especially aspects

NOTE Confidence: 0.822189974285714

 $00{:}07{:}19.604 \dashrightarrow 00{:}07{:}22.430$ of even of drug seeking behavior.

 $00:07:22.430 \rightarrow 00:07:25.358$ But we were surprised when we saw these

NOTE Confidence: 0.822189974285714

 $00:07:25.358 \rightarrow 00:07:27.699$ really profound changes of epigenetics.

NOTE Confidence: 0.822189974285714

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

NOTE Confidence: 0.822189974285714

 $00:07:29.228 \rightarrow 00:07:33.048$ these epigenetic marks were were.

NOTE Confidence: 0.822189974285714

 $00:07:33.050 \rightarrow 00:07:35.066$ 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

 $00:07:37.350 \longrightarrow 00:07:38.490$ developmental cannabis studies.

NOTE Confidence: 0.822189974285714

 $00:07:38.490 \rightarrow 00:07:41.292$ Because we focused a lot initially

NOTE Confidence: 0.822189974285714

 $00{:}07{:}41.292 \dashrightarrow 00{:}07{:}43.926$ in trying to understand the

NOTE Confidence: 0.822189974285714

 $00:07:43.926 \rightarrow 00:07:45.978$ individual vulnerability that.

NOTE Confidence: 0.822189974285714

 $00:07:45.980 \longrightarrow 00:07:48.440$ 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

 $00:07:53.294 \dashrightarrow 00:07:55.119$ we focus initially on genetics.

NOTE Confidence: 0.822189974285714

 $00:07:55.120 \rightarrow 00:07:58.096$ But the environment of this complex

 $00:07:58.096 \rightarrow 00:08:00.680$ disorder addiction plays a critical

NOTE Confidence: 0.822189974285714

 $00{:}08{:}00{.}680 \dashrightarrow 00{:}08{:}03{.}440$ role and it plays a critical role in

NOTE Confidence: 0.822189974285714

 $00:08:03.440 \dashrightarrow 00:08:06.108$ being able to change gene expression.

NOTE Confidence: 0.822189974285714

 $00{:}08{:}06{.}110 \dashrightarrow 00{:}08{:}08{.}354$ And and in fact sometimes can

NOTE Confidence: 0.822189974285714

 $00:08:08.354 \rightarrow 00:08:09.850$ override these genetic blueprints.

NOTE Confidence: 0.822189974285714

 $00:08:09.850 \longrightarrow 00:08:11.691$ So genes that should be closed are

NOTE Confidence: 0.822189974285714

 $00{:}08{:}11.691 \dashrightarrow 00{:}08{:}13.821$ now turned on and genes that are that

NOTE Confidence: 0.822189974285714

 $00:08:13.821 \longrightarrow 00:08:15.990$ should be turned on and now turned off.

NOTE Confidence: 0.822189974285714

 $00{:}08{:}15{.}990 \dashrightarrow 00{:}08{:}19{.}570$ And there are numerous epigenetic

NOTE Confidence: 0.822189974285714

 $00:08:19.570 \rightarrow 00:08:21.434$ Marks and epigenetic mechanisms.

NOTE Confidence: 0.822189974285714

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

NOTE Confidence: 0.822189974285714

 $00{:}08{:}22.370 \dashrightarrow 00{:}08{:}24.280$ we've only touching the surface

NOTE Confidence: 0.822189974285714

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

NOTE Confidence: 0.822189974285714

 $00{:}08{:}25{.}810 \dashrightarrow 00{:}08{:}28{.}042$ but we had a fundamental understanding

NOTE Confidence: 0.822189974285714

 $00{:}08{:}28{.}042 \dashrightarrow 00{:}08{:}30{.}432$ of what some of these epigenetic

 $00:08:30.432 \longrightarrow 00:08:33.330$ marks may mean on a functional level.

NOTE Confidence: 0.822189974285714

 $00:08:33.330 \longrightarrow 00:08:36.249$ So, for example, if you have methylation.

NOTE Confidence: 0.822189974285714

 $00{:}08{:}36{.}250 \dashrightarrow 00{:}08{:}39{.}046$ DNA often that was a repressive

NOTE Confidence: 0.822189974285714

 $00:08:39.046 \rightarrow 00:08:41.802$ mark and would reduce transcription,

NOTE Confidence: 0.822189974285714

 $00:08:41.802 \rightarrow 00:08:43.830$ while for example,

NOTE Confidence: 0.822189974285714

 $00{:}08{:}43.830 \dashrightarrow 00{:}08{:}46.006$ 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

 $00:08:49.270 \longrightarrow 00:08:52.066$ 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

 $00{:}08{:}53{.}994 \dashrightarrow 00{:}08{:}55{.}809$ and assimilation would open up

NOTE Confidence: 0.822189974285714

 $00{:}08{:}55{.}809 \dashrightarrow 00{:}08{:}58{.}068$ those the those regions of the

NOTE Confidence: 0.822189974285714

 $00{:}08{:}58{.}068 \dashrightarrow 00{:}08{:}59{.}928$ gene and turn on transcription.

NOTE Confidence: 0.822189974285714

 $00:08:59.930 \rightarrow 00:09:01.295$ And depending on where methylation

NOTE Confidence: 0.822189974285714

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

NOTE Confidence: 0.822189974285714

 $00:09:02.120 \longrightarrow 00:09:05.395$ you could also have transcriptional

NOTE Confidence: 0.822189974285714

 $00:09:05.395 \rightarrow 00:09:06.050$ repression.

 $00:09:06.050 \dashrightarrow 00:09:08.498$ And what we saw in the brains of heroin

NOTE Confidence: 0.822189974285714

 $00{:}09{:}08{.}498 \dashrightarrow 00{:}09{:}11{.}017$ 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

 $00:09:13.200 \rightarrow 00:09:15.285$ it was predictive of this

NOTE Confidence: 0.822189974285714

 $00:09:15.285 \dashrightarrow 00:09:16.536$ enhanced transcriptional state.

NOTE Confidence: 0.822189974285714

 $00:09:16.540 \rightarrow 00:09:21.430$ But it was specific to certain gene.

NOTE Confidence: 0.822189974285714

 $00{:}09{:}21.430 \dashrightarrow 00{:}09{:}23.945$ 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

 $00:09:26.460 \longrightarrow 00:09:28.100$ so these epigenetic marks

NOTE Confidence: 0.822189974285714

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

NOTE Confidence: 0.822189974285714

 $00:09:29.740 \longrightarrow 00:09:32.132$ Inherent users with glutamatergic

NOTE Confidence: 0.822189974285714

 $00{:}09{:}32{.}132 \dashrightarrow 00{:}09{:}35{.}122$ genes or synaptic plasticity genes

NOTE Confidence: 0.822189974285714

 $00:09:35.122 \rightarrow 00:09:39.038$ and it was very specific where these

NOTE Confidence: 0.822189974285714

 $00{:}09{:}39{.}038 \dashrightarrow 00{:}09{:}41.729$ epigenetic tags were predicted to occur,

NOTE Confidence: 0.822189974285714

 $00:09:41.729 \longrightarrow 00:09:44.130$ and a lot of the the genetic

 $00:09:44.202 \rightarrow 00:09:46.846$ changes related to, for example,

NOTE Confidence: 0.822189974285714

 $00{:}09{:}46.846 \dashrightarrow 00{:}09{:}49.418$ a civilation and assimilation

NOTE Confidence: 0.822189974285714

 $00:09:49.418 \longrightarrow 00:09:51.990$ of the the lysine.

NOTE Confidence: 0.822189974285714

 $00:09:51.990 \longrightarrow 00:09:52.695$ In a region,

NOTE Confidence: 0.822189974285714

 $00:09:52.695 \rightarrow 00:09:54.737$ 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

 $00{:}09{:}57{.}455 \dashrightarrow 00{:}10{:}00{.}905$ regulation of gene transcription and it

NOTE Confidence: 0.822189974285714

 $00{:}10{:}00{.}905 \dashrightarrow 00{:}10{:}04.060$ related to their years of heroin use.

NOTE Confidence: 0.822189974285714

 $00{:}10{:}04.060 \dashrightarrow 00{:}10{:}06.904$ 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

 $00:10:09.020 \longrightarrow 00:10:11.270$ and we saw consistently this.

NOTE Confidence: 0.89750624

 $00{:}10{:}11{.}270 \dashrightarrow 00{:}10{:}15{.}438$ This opening of the transcriptome in in

NOTE Confidence: 0.89750624

 $00{:}10{:}15{.}438 \dashrightarrow 00{:}10{:}17{.}426$ relation to the years of heroin news

NOTE Confidence: 0.89750624

 $00{:}10{:}17{.}426 \dashrightarrow 00{:}10{:}19{.}840$ and especially cassette around these

NOTE Confidence: 0.89750624

 $00{:}10{:}19{.}840 \dashrightarrow 00{:}10{:}21{.}908$ synaptic plasticity related genes.

NOTE Confidence: 0.89750624

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

 $00{:}10{:}23.611 \dashrightarrow 00{:}10{:}25.765$ life and we don't know that much about

NOTE Confidence: 0.89750624

 $00{:}10{:}25.765 \dashrightarrow 00{:}10{:}27.479$ all their lives just about their

NOTE Confidence: 0.89750624

 $00{:}10{:}27{.}479 \dashrightarrow 00{:}10{:}29{.}207$ toxicology and often like I said,

NOTE Confidence: 0.89750624

 $00:10:29.210 \longrightarrow 00:10:30.841$ 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

 $00{:}10{:}32{.}260 \dashrightarrow 00{:}10{:}34{.}724$ we use our animal models where animals

NOTE Confidence: 0.89750624

 $00{:}10{:}34.724 \dashrightarrow 00{:}10{:}36.882$ will self administer heroin and we

NOTE Confidence: 0.89750624

 $00:10:36.882 \rightarrow 00:10:38.958$ could actually replicate where in the

NOTE Confidence: 0.89750624

 $00{:}10{:}38{.}958 \dashrightarrow 00{:}10{:}41{.}216$ genome or in the in the transcription.

NOTE Confidence: 0.89750624

 $00:10:41.220 \longrightarrow 00:10:43.159$ Say that we saw this gene expression

NOTE Confidence: 0.89750624

 $00{:}10{:}43.159 \dashrightarrow 00{:}10{:}45.205$ changes and when we looked at the

NOTE Confidence: 0.89750624

 $00{:}10{:}45.205 \dashrightarrow 00{:}10{:}46.655$ epigenetic tags in these regions,

NOTE Confidence: 0.89750624

 $00:10:46.660 \rightarrow 00:10:49.300$ they correlated exactly to what we saw in,

NOTE Confidence: 0.89750624

 $00:10:49.300 \longrightarrow 00:10:50.246$ for example,

NOTE Confidence: 0.89750624

 $00{:}10{:}50.246 \dashrightarrow 00{:}10{:}52.679$ their civilation of these these

 $00:10:52.679 \rightarrow 00:10:55.374$ 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

 $00{:}10{:}58{.}559 \dashrightarrow 00{:}11{:}01{.}365$ I'm not getting as as detail I know

NOTE Confidence: 0.89750624

 $00:11:01.365 \rightarrow 00:11:04.467$ because even more broad clinical audience.

NOTE Confidence: 0.89750624

 $00{:}11{:}04.470 \dashrightarrow 00{:}11{:}06.057$ But what is?

NOTE Confidence: 0.89750624

 $00{:}11{:}06.057 \dashrightarrow 00{:}11{:}09.760$ What does that epigenetic change really mean?

NOTE Confidence: 0.89750624

 $00{:}11{:}09{.}760 \dashrightarrow 00{:}11{:}12{.}640$ So for for the histones in terms

NOTE Confidence: 0.89750624

 $00:11:12.640 \rightarrow 00:11:16.561$ of we have tags that are put on these

NOTE Confidence: 0.89750624

 $00:11:16.561 \rightarrow 00:11:19.960$ histores and they're they're called writers.

NOTE Confidence: 0.89750624

 $00{:}11{:}19{.}960 \dashrightarrow 00{:}11{:}21{.}922$ These enzymes and we have others

NOTE Confidence: 0.89750624

 $00:11:21.922 \longrightarrow 00:11:23.860$ that take the these tags off,

NOTE Confidence: 0.89750624

 $00{:}11{:}23.860 \dashrightarrow 00{:}11{:}26.844$ and we then have a readers that must

NOTE Confidence: 0.89750624

 $00:11:26.844 \longrightarrow 00:11:29.382$ give information to the system as to

NOTE Confidence: 0.89750624

 $00{:}11{:}29{.}382 \dashrightarrow 00{:}11{:}31{.}324$ 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

 $00{:}11{:}33{.}195 \dashrightarrow 00{:}11{:}35{.}370$ And for assimilation the bromodomain

- NOTE Confidence: 0.89750624
- $00:11:35.370 \longrightarrow 00:11:36.820$ 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
- $00{:}11{:}39{.}450 \dashrightarrow 00{:}11{:}40{.}635$ 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
- $00{:}11{:}45.162 \dashrightarrow 00{:}11{:}46.776$ three and four.
- NOTE Confidence: 0.89750624
- $00:11:46.780 \rightarrow 00:11:48.425$ And there's also one in the testes,
- NOTE Confidence: 0.89750624
- $00:11:48.430 \longrightarrow 00:11:50.725$ but we only have 3 at least so far
- NOTE Confidence: 0.89750624
- $00:11:50.725 \longrightarrow 00:11:52.889$ that was identified in the brain,
- NOTE Confidence: 0.89750624
- $00:11:52.890 \rightarrow 00:11:55.860$ and these are expressed in numerous
- NOTE Confidence: 0.89750624
- $00:11:55.860 \longrightarrow 00:11:56.850$ brain regions.
- NOTE Confidence: 0.89750624
- $00{:}11{:}56{.}850 \dashrightarrow 00{:}11{:}57{.}754$ BRD 2-3 and four.
- NOTE Confidence: 0.89750624
- $00{:}11{:}57{.}754 \dashrightarrow 00{:}12{:}00{.}190$ But when we look in the brains both in in
- NOTE Confidence: 0.89750624
- $00{:}12{:}00{.}190 \dashrightarrow 00{:}12{:}02{.}549$ human hair and users and and animal models,
- NOTE Confidence: 0.89750624
- $00{:}12{:}02{.}550 \dashrightarrow 00{:}12{:}05{.}007$ we didn't see changes in BRD two or three.
- NOTE Confidence: 0.89750624

 $00:12:05.010 \rightarrow 00:12:08.597$ What we saw were changes in beer D4 and

NOTE Confidence: 0.89750624

 $00{:}12{:}08.597 \dashrightarrow 00{:}12{:}11.519$ in different cohorts that we study.

NOTE Confidence: 0.89750624

 $00{:}12{:}11{.}520 \dashrightarrow 00{:}12{:}11{.}958$ So.

NOTE Confidence: 0.89750624

 $00{:}12{:}11{.}958 \dashrightarrow 00{:}12{:}14{.}586$ The thing that was also fascinating

NOTE Confidence: 0.89750624

 $00:12:14.586 \longrightarrow 00:12:17.308$ 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

 $00:12:20.593 \rightarrow 00:12:23.383$ 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

 $00{:}12{:}26.610 \dashrightarrow 00{:}12{:}27.994$ such as DLG 4,

NOTE Confidence: 0.89750624

 $00:12:27.994 \longrightarrow 00:12:30.070$ which is the gene that encodes

NOTE Confidence: 0.89750624

 $00{:}12{:}30.070 \dashrightarrow 00{:}12{:}33.780$ PSD 95 this postsynaptic density.

NOTE Confidence: 0.89750624

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

NOTE Confidence: 0.89750624

 $00:12:34.150 \longrightarrow 00:12:34.890$ So again,

NOTE Confidence: 0.89750624

 $00{:}12{:}34.890 \dashrightarrow 00{:}12{:}37.480$ every single thing told us that there

NOTE Confidence: 0.89750624

 $00{:}12{:}37{.}550 \dashrightarrow 00{:}12{:}40{.}020$ was something really interesting about

NOTE Confidence: 0.89750624

 $00:12:40.020 \rightarrow 00:12:43.184$ the BRD 4, the Bromodomain readers.

 $00:12:43.184 \rightarrow 00:12:45.848$ So the thing that's very important

NOTE Confidence: 0.89750624

 $00{:}12{:}45{.}848 \dashrightarrow 00{:}12{:}47{.}927$ about epigenetics and at

NOTE Confidence: 0.89750624

 $00{:}12{:}47{.}927 \dashrightarrow 00{:}12{:}50{.}272$ least at the time when we started

NOTE Confidence: 0.89750624

 $00:12:50.272 \rightarrow 00:12:52.629$ studying this was although now in

NOTE Confidence: 0.89750624

 $00{:}12{:}52.629 \dashrightarrow 00{:}12{:}55.184$ neuroscience more and more focus is

NOTE Confidence: 0.89750624

 $00{:}12{:}55{.}184 \dashrightarrow 00{:}12{:}57{.}600$ looking at epigenetic mechanisms.

NOTE Confidence: 0.89750624

 $00:12:57.600 \longrightarrow 00:12:59.682$ The greatest information that we know

NOTE Confidence: 0.89750624

 $00:12:59.682 \rightarrow 00:13:01.900$ really comes from the cancer field.

NOTE Confidence: 0.89750624

 $00:13:01.900 \rightarrow 00:13:05.180$ And there they've been able to identify many,

NOTE Confidence: 0.89750624

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

NOTE Confidence: 0.878953266

 $00{:}13{:}09{.}890 \dashrightarrow 00{:}13{:}13{.}110$ Chemicals that can inhibit specific

NOTE Confidence: 0.878953266

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

NOTE Confidence: 0.878953266

 $00{:}13{:}15.698 \dashrightarrow 00{:}13{:}17.639$ certain epigenetic mechanisms.

NOTE Confidence: 0.878953266

 $00{:}13{:}17.640 \dashrightarrow 00{:}13{:}20.058$ Because the cancer is definitely a

NOTE Confidence: 0.878953266

 $00{:}13{:}20.058 \dashrightarrow 00{:}13{:}22.070$ disorder of epigenetic gone awry,

 $00:13:22.070 \rightarrow 00:13:24.670$ so we were able to leverage what was

NOTE Confidence: 0.878953266

 $00{:}13{:}24.670 \dashrightarrow 00{:}13{:}26.639$ being developed at that time in terms

NOTE Confidence: 0.878953266

 $00{:}13{:}26.639 \dashrightarrow 00{:}13{:}28.854$ of some of the the chemicals to see

NOTE Confidence: 0.878953266

 $00:13:28.854 \rightarrow 00:13:31.392$ whether or not if we could inhibit BRD,

NOTE Confidence: 0.878953266

 $00:13:31.392 \rightarrow 00:13:33.989$ we had hoped to inhibit bird for,

NOTE Confidence: 0.878953266

 $00:13:33.990 \longrightarrow 00:13:34.850$ specifically.

NOTE Confidence: 0.878953266

 $00:13:34.850 \rightarrow 00:13:39.834$ Could that itself decrease or heroin self?

NOTE Confidence: 0.878953266

 $00:13:39.834 \longrightarrow 00:13:41.544$ Administration and at the time,

NOTE Confidence: 0.878953266

 $00{:}13{:}41{.}550 \dashrightarrow 00{:}13{:}43{.}554$ the prototypical BRD inhibitor,

NOTE Confidence: 0.878953266

 $00:13:43.554 \rightarrow 00:13:46.560$ they would promote it as BRD.

NOTE Confidence: 0.878953266

 $00:13:46.560 \longrightarrow 00:13:47.376$ 4 inhibitor.

NOTE Confidence: 0.878953266

 $00{:}13{:}47{.}376 \dashrightarrow 00{:}13{:}49{.}824$ It really was not selected because

NOTE Confidence: 0.878953266

 $00:13:49.824 \longrightarrow 00:13:52.196$ 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

 $00{:}13{:}53{.}541 \dashrightarrow 00{:}13{:}56{.}570$ so we nevertheless looked at the JQ

NOTE Confidence: 0.878953266

 $00:13:56.570 \rightarrow 00:13:58.545$ one was approachable the inhibitor

- NOTE Confidence: 0.878953266
- $00:13:58.545 \rightarrow 00:14:01.440$ at a time in our animal models,
- NOTE Confidence: 0.878953266
- $00:14:01.440 \rightarrow 00:14:02.422$ and interestingly,
- NOTE Confidence: 0.878953266
- $00:14:02.422 \longrightarrow 00:14:05.859$ when we gave it into the striatum,
- NOTE Confidence: 0.878953266
- $00:14:05.860 \rightarrow 00:14:08.602$ we could reduce heroin self administration
- NOTE Confidence: 0.878953266
- $00:14:08.602 \rightarrow 00:14:10.430$ and heroin seeking behavior.
- NOTE Confidence: 0.878953266
- $00:14:10.430 \longrightarrow 00:14:12.654$ But the goal long term goal is to
- NOTE Confidence: 0.878953266
- $00:14:12.654 \rightarrow 00:14:14.849$ be able to develop medications.
- NOTE Confidence: 0.878953266
- $00:14:14.850 \longrightarrow 00:14:16.698$ 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
- $00:14:21.230 \rightarrow 00:14:23.760$ we could significantly reduce heroin
- NOTE Confidence: 0.878953266
- $00{:}14{:}23.760 \dashrightarrow 00{:}14{:}26.930$ self administration behavior in the animals.
- NOTE Confidence: 0.878953266
- $00{:}14{:}26{.}930 \dashrightarrow 00{:}14{:}29{.}190$ So.
- NOTE Confidence: 0.878953266
- $00{:}14{:}29{.}190 \dashrightarrow 00{:}14{:}32{.}370$ The the leveraging you know the
- NOTE Confidence: 0.878953266
- $00{:}14{:}32{.}370 \dashrightarrow 00{:}14{:}34{.}120$ looking at the postmortems brains
- NOTE Confidence: 0.878953266

 $00:14:34.120 \longrightarrow 00:14:36.657$ of heroin users you were able to

NOTE Confidence: 0.878953266

 $00{:}14{:}36.657 \dashrightarrow 00{:}14{:}38.467$ see that these epigenetic changes,

NOTE Confidence: 0.878953266

 $00{:}14{:}38{.}470 \dashrightarrow 00{:}14{:}40{.}620$ especially those that related to

NOTE Confidence: 0.878953266

 $00:14:40.620 \rightarrow 00:14:43.660$ genes as part of synaptic plasticity,

NOTE Confidence: 0.878953266

 $00:14:43.660 \rightarrow 00:14:45.570$ especially these little mergent genes,

NOTE Confidence: 0.878953266

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

NOTE Confidence: 0.878953266

 $00:14:46.743 \rightarrow 00:14:49.480$ with the years of heroin use and

NOTE Confidence: 0.878953266

 $00:14:49.546 \rightarrow 00:14:51.846$ inhibiting it we could inhibit

NOTE Confidence: 0.878953266

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

NOTE Confidence: 0.878953266

 $00:14:53.226 \rightarrow 00:14:55.289$ behavior and more importantly,

NOTE Confidence: 0.878953266

 $00:14:55.290 \longrightarrow 00:14:56.628$ heroin seeking behavior.

NOTE Confidence: 0.869300692166667

 $00:14:58.900 \rightarrow 00:15:01.378$ Unfortunately we have tried for many

NOTE Confidence: 0.869300692166667

 $00{:}15{:}01{.}378 \dashrightarrow 00{:}15{:}05{.}069$ years to try to develop a or to obtain

NOTE Confidence: 0.869300692166667

 $00{:}15{:}05{.}069 \dashrightarrow 00{:}15{:}07{.}847$ even a specific beauty for inhibitor and

NOTE Confidence: 0.869300692166667

 $00{:}15{:}07.847 \dashrightarrow 00{:}15{:}11.220$ 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

 $00:15:14.740 \longrightarrow 00:15:18.260$ give these this talk of what our our,

NOTE Confidence: 0.869300692166667

 $00:15:18.260 \rightarrow 00:15:21.900$ you know these BT family of inhibitors,

NOTE Confidence: 0.869300692166667

 $00:15:21.900 \rightarrow 00:15:23.028$ how they're being developed

NOTE Confidence: 0.869300692166667

 $00:15:23.028 \longrightarrow 00:15:24.156$ in the cancer field.

NOTE Confidence: 0.869300692166667

 $00{:}15{:}24.160 \dashrightarrow 00{:}15{:}25.936$ But we still have not been able to

NOTE Confidence: 0.869300692166667

 $00{:}15{:}25{.}936 \dashrightarrow 00{:}15{:}27{.}296$ find some that actually penetrate

NOTE Confidence: 0.869300692166667

 $00:15:27.296 \longrightarrow 00:15:29.012$ the brain on these the BRD.

NOTE Confidence: 0.869300692166667

 $00:15:29.020 \rightarrow 00:15:32.506$ What specific purity for inhibitors that

NOTE Confidence: 0.869300692166667

 $00:15:32.510 \rightarrow 00:15:35.030$ passes the blood brain barrier effectively?

NOTE Confidence: 0.869300692166667

 $00:15:35.030 \rightarrow 00:15:37.640$ And so we're still trying,

NOTE Confidence: 0.869300692166667

 $00:15:37.640 \longrightarrow 00:15:39.566$ but it's important to also emphasize

NOTE Confidence: 0.869300692166667

 $00{:}15{:}39{.}566 \dashrightarrow 00{:}15{:}41{.}794$ that it's not only our group that

NOTE Confidence: 0.869300692166667

 $00{:}15{:}41.794 \dashrightarrow 00{:}15{:}43.838$ has seen these changes in beard for

NOTE Confidence: 0.869300692166667

 $00{:}15{:}43{.}903 \dashrightarrow 00{:}15{:}46{.}008$ relevant to substance use disorders,

NOTE Confidence: 0.869300692166667

 $00:15:46.010 \longrightarrow 00:15:47.970$ other groups have seen that.

 $00{:}15{:}47{.}970$ --> $00{:}15{:}52{.}072$ In fact you cocaine self administration will

NOTE Confidence: 0.869300692166667

 $00:15:52.072 \rightarrow 00:15:55.608$ also increase variety for and inhibiting.

NOTE Confidence: 0.869300692166667

 $00{:}15{:}55{.}610 \dashrightarrow 00{:}15{:}57{.}955$ Giving the JQ one inhibitor the B

NOTE Confidence: 0.869300692166667

 $00:15:57.955 \rightarrow 00:16:00.109$ inhibitor also will decrease cocaine,

NOTE Confidence: 0.869300692166667

 $00{:}16{:}00{.}110 \dashrightarrow 00{:}16{:}01{.}615$ place preference and cocaine self

NOTE Confidence: 0.869300692166667

 $00{:}16{:}01{.}615 \dashrightarrow 00{:}16{:}03{.}469$ administration and I think that that's

NOTE Confidence: 0.869300692166667

 $00:16:03.469 \longrightarrow 00:16:04.974$ really important because when we

NOTE Confidence: 0.869300692166667

 $00{:}16{:}04{.}974 \dashrightarrow 00{:}16{:}06{.}448$ 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

 $00{:}16{:}08{.}224 \dashrightarrow 00{:}16{:}10{.}652$ most selective thing or I think in

NOTE Confidence: 0.869300692166667

 $00:16:10.652 \rightarrow 00:16:13.437$ psychiatry in general I think you know

NOTE Confidence: 0.869300692166667

 $00{:}16{:}13{.}437 \dashrightarrow 00{:}16{:}15{.}927$ the the strongest antagonists of the

NOTE Confidence: 0.869300692166667

 $00:16:15.927 \rightarrow 00:16:18.428$ dopamine receptor and and selectivity,

NOTE Confidence: 0.869300692166667

 $00{:}16{:}18{.}430 \dashrightarrow 00{:}16{:}20{.}922$ but for substance use disorders we know

NOTE Confidence: 0.869300692166667

 $00:16:20.922 \rightarrow 00:16:23.588$ that many people are polysubstance users.

NOTE Confidence: 0.869300692166667

 $00{:}16{:}23.590 \dashrightarrow 00{:}16{:}25.150$ So for me the fact that

- NOTE Confidence: 0.869300692166667
- $00:16:25.150 \longrightarrow 00:16:26.190$ we see some commonality.
- NOTE Confidence: 0.869300692166667
- $00:16:26.190 \longrightarrow 00:16:29.376$ 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
- $00:16:31.774 \rightarrow 00:16:33.588$ 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
- $00:16:38.760 \longrightarrow 00:16:40.340$ you know, in developing medications
- NOTE Confidence: 0.841385738333333
- $00:16:40.340 \longrightarrow 00:16:41.920$ based on what we've seen,
- NOTE Confidence: 0.841385738333333
- $00:16:41.920 \longrightarrow 00:16:43.390$ the human brain and how
- NOTE Confidence: 0.841385738333333
- $00:16:43.390 \longrightarrow 00:16:44.860$ 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
- $00{:}16{:}47{.}308 \dashrightarrow 00{:}16{:}49{.}120$ epigenetics and synaptic plasticity,
- NOTE Confidence: 0.841385738333333
- $00{:}16{:}49{.}120 \dashrightarrow 00{:}16{:}52{.}156$ and the reason is once again.
- NOTE Confidence: 0.841385738333333
- $00{:}16{:}52{.}160 \dashrightarrow 00{:}16{:}55{.}282$ 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
- $00{:}16{:}57{.}478 \dashrightarrow 00{:}16{:}59{.}969$ you know when we we looked at the
- NOTE Confidence: 0.841385738333333

 $00:16:59.969 \rightarrow 00:17:01.629$ gene expression that transcriptome

NOTE Confidence: 0.841385738333333

 $00{:}17{:}01.629 \dashrightarrow 00{:}17{:}04.919$ we were able to see these epigenetic

NOTE Confidence: 0.841385738333333

 $00{:}17{:}04{.}920 \dashrightarrow 00{:}17{:}06{.}830$ genes related to epigenetic mechanisms

NOTE Confidence: 0.841385738333333

 $00:17:06.830 \longrightarrow 00:17:08.358$ and the synaptic plasticity.

NOTE Confidence: 0.841385738333333

 $00:17:08.360 \longrightarrow 00:17:10.672$ But you can also look at the epigenome

NOTE Confidence: 0.841385738333333

 $00{:}17{:}10.672 \dashrightarrow 00{:}17{:}12.460$ itself in an agnostic manner.

NOTE Confidence: 0.841385738333333

 $00{:}17{:}12.460 \dashrightarrow 00{:}17{:}14.782$ You can actually sequence the the

NOTE Confidence: 0.841385738333333

 $00{:}17{:}14.782 \dashrightarrow 00{:}17{:}17.402$ 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

 $00:17:19.793 \rightarrow 00:17:22.117$ assay for transposase accessible.

NOTE Confidence: 0.841385738333333

 $00:17:22.120 \longrightarrow 00:17:23.074$ Something basically,

NOTE Confidence: 0.841385738333333

 $00{:}17{:}23.074 \dashrightarrow 00{:}17{:}25.936$ you're looking at chromatin state looking

NOTE Confidence: 0.841385738333333

 $00{:}17{:}25{.}936 \dashrightarrow 00{:}17{:}28{.}850$ at where in the where in the epigenome,

NOTE Confidence: 0.841385738333333

 $00:17:28.850 \rightarrow 00:17:31.070$ maybe in the chromatin is open,

NOTE Confidence: 0.841385738333333

 $00:17:31.070 \rightarrow 00:17:34.122$ and therefore would be associated with gene

NOTE Confidence: 0.841385738333333

 $00:17:34.122 \rightarrow 00:17:36.567$ 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
- $00:17:38.642 \rightarrow 00:17:41.750$ because normally when you look at
- NOTE Confidence: 0.841385738333333
- $00{:}17{:}41{.}831 \dashrightarrow 00{:}17{:}44{.}514$ 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
- $00:17:48.632 \rightarrow 00:17:50.048$ we might have chosen,
- NOTE Confidence: 0.841385738333333
- $00:17:50.050 \rightarrow 00:17:51.506$ like acetylation of lysine.
- NOTE Confidence: 0.841385738333333
- $00:17:51.506 \longrightarrow 00:17:54.124$ 27 that we showed that was changed
- NOTE Confidence: 0.841385738333333
- $00:17:54.124 \rightarrow 00:17:56.320$ in the brains of heroin users,
- NOTE Confidence: 0.841385738333333
- $00{:}17{:}56{.}320 \dashrightarrow 00{:}17{:}58{.}608$ but we know it's the combination of a
- NOTE Confidence: 0.841385738333333
- $00:17:58.608 \rightarrow 00:18:00.948$ number of epigenetic marks that will lead
- NOTE Confidence: 0.841385738333333
- $00{:}18{:}00{.}948 \dashrightarrow 00{:}18{:}03{.}164$ to these changes in gene transcription
- NOTE Confidence: 0.841385738333333
- $00{:}18{:}03{.}164 \dashrightarrow 00{:}18{:}04{.}964$ and therefore obviously downstream
- NOTE Confidence: 0.841385738333333
- $00{:}18{:}04{.}964 \dashrightarrow 00{:}18{:}07{.}682$ changes in in protein and function.
- NOTE Confidence: 0.841385738333333
- $00{:}18{:}07{.}682 \dashrightarrow 00{:}18{:}10{.}916$ So if we look agnostically using this,
- NOTE Confidence: 0.841385738333333

 $00:18:10.920 \rightarrow 00:18:13.993$ a taxi that has actually been extremely

NOTE Confidence: 0.841385738333333

 $00:18:13.993 \rightarrow 00:18:16.435$ 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

 $00:18:19.427 \rightarrow 00:18:22.295$ most significantly changed with hearing news.

NOTE Confidence: 0.841385738333333

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

NOTE Confidence: 0.841385738333333

 $00:18:22.936 \rightarrow 00:18:24.526$ this technique allows a something

NOTE Confidence: 0.841385738333333

 $00:18:24.526 \longrightarrow 00:18:26.177$ for me that's important for

NOTE Confidence: 0.841385738333333

 $00:18:26.177 \rightarrow 00:18:27.469$ 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

 $00:18:30.870 \rightarrow 00:18:33.723$ and this way we can look at different cells.

NOTE Confidence: 0.841385738333333

 $00:18:33.730 \longrightarrow 00:18:35.710$ Cell types in the human brain.

NOTE Confidence: 0.841385738333333

 $00:18:35.710 \longrightarrow 00:18:37.432$ 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

 $00:18:39.110 \longrightarrow 00:18:41.258$ not looking at specific neurons and

NOTE Confidence: 0.841385738333333

 $00:18:41.258 \rightarrow 00:18:43.890$ specific non glia non neuronal subtypes.

NOTE Confidence: 0.841385738333333

 $00:18:43.890 \rightarrow 00:18:46.590$ 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.

NOTE Confidence: 0.841385738333333

 $00:18:49.490 \longrightarrow 00:18:52.310$ A previous student who's now.

NOTE Confidence: 0.841385738333333

 $00:18:52.310 \rightarrow 00:18:55.820$ Going for his first independent position,

NOTE Confidence: 0.841385738333333

 $00{:}18{:}55{.}820 \dashrightarrow 00{:}18{:}59{.}951$ America Avari in in using the taxi we could

NOTE Confidence: 0.841385738333333

 $00:18:59.951 \rightarrow 00:19:04.318$ see that indeed we were able to dissociate.

NOTE Confidence: 0.841385738333333

 $00:19:04.320 \rightarrow 00:19:06.812$ Which epigenetic signatures that

NOTE Confidence: 0.841385738333333

 $00{:}19{:}06{.}812 \dashrightarrow 00{:}19{:}09{.}304$ dissociated neurons from glia.

NOTE Confidence: 0.841385738333333

 $00:19:09.310 \longrightarrow 00:19:13.886$ But we could also see those that dissociated.

NOTE Confidence: 0.841385738333333

 $00:19:13.890 \longrightarrow 00:19:16.767$ Up here with disorders heroin use this.

NOTE Confidence: 0.841385738333333

 $00:19:16.770 \longrightarrow 00:19:18.744$ The dissociated heroin use in neurons

NOTE Confidence: 0.841385738333333

 $00:19:18.744 \rightarrow 00:19:21.334$ and what we saw specifically was that

NOTE Confidence: 0.841385738333333

 $00:19:21.334 \rightarrow 00:19:23.752$ the gene ontology of where these

NOTE Confidence: 0.841385738333333

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

NOTE Confidence: 0.841385738333333

 $00{:}19{:}25{.}913 \dashrightarrow 00{:}19{:}28{.}445$ shows really strong dys regulation on an

NOTE Confidence: 0.841385738333333

 $00{:}19{:}28{.}450 \dashrightarrow 00{:}19{:}31{.}610$ epigenetic level of synaptic plasticity.

- 00:19:31.610 --> 00:19:32.301 Again,
- NOTE Confidence: 0.841385738333333
- $00:19:32.301 \rightarrow 00:19:35.065$ these little meteorologic postsynaptic
- NOTE Confidence: 0.841385738333333
- 00:19:35.065 --> 00:19:37.426 density dendritic changes and
- NOTE Confidence: 0.841385738333333
- $00:19:37.426 \rightarrow 00:19:39.866$ what were the genes changed?
- NOTE Confidence: 0.841385738333333
- $00:19:39.870 \longrightarrow 00:19:42.080$ The top gene was Finn.
- NOTE Confidence: 0.841385738333333
- $00:19:42.080 \rightarrow 00:19:44.540$ And that was fascinating for us,
- NOTE Confidence: 0.841385738333333
- $00{:}19{:}44{.}540 \dashrightarrow 00{:}19{:}46{.}500$ because we had never studied fan and
- NOTE Confidence: 0.841385738333333
- $00:19:46.500 \rightarrow 00:19:48.049$ obviously it yellow come to that.
- NOTE Confidence: 0.841385738333333
- $00:19:48.050 \rightarrow 00:19:49.688$ You guys have been studying it for
- NOTE Confidence: 0.841385738333333
- $00:19:49.688 \longrightarrow 00:19:53.065$ a while and the thing also was
- NOTE Confidence: 0.841385738333333
- $00{:}19{:}53.065 \dashrightarrow 00{:}19{:}55.389$ that the this this.
- NOTE Confidence: 0.841385738333333
- $00:19:55.390 \rightarrow 00:19:58.190$ 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
- $00:20:01.110 \rightarrow 00:20:04.785$ of the variance for identifying heroin users.
- NOTE Confidence: 0.937294331428571
- $00:20:04.790 \rightarrow 00:20:07.220$ We were able to to show that my student Tony
- NOTE Confidence: 0.937294331428571
- $00:20:07.283 \rightarrow 00:20:09.715$ Roman was able to show that it's functional.

 $00{:}20{:}09{.}720 \dashrightarrow 00{:}20{:}12{.}198$ The change this this enhancer region that

NOTE Confidence: 0.937294331428571

 $00:20:12.198 \longrightarrow 00:20:14.992$ we saw had the greatest chromatin change

NOTE Confidence: 0.937294331428571

 $00:20:14.992 \rightarrow 00:20:18.243$ in Harry Newsers in the stratum and we were

NOTE Confidence: 0.937294331428571

 $00:20:18.243 \rightarrow 00:20:20.949$ able to see also that it was self specific,

NOTE Confidence: 0.937294331428571

 $00:20:20.950 \longrightarrow 00:20:23.254$ at least that we didn't see these changes

NOTE Confidence: 0.937294331428571

 $00:20:23.254 \rightarrow 00:20:26.626$ 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

 $00{:}20{:}28{.}370 \dashrightarrow 00{:}20{:}29{.}490$ As I said, you know.

NOTE Confidence: 0.937294331428571

 $00{:}20{:}29{.}490 \dashrightarrow 00{:}20{:}34{.}200$ For Yale, I know many of you Vandyke and

NOTE Confidence: 0.937294331428571

 $00:20:34.200 \longrightarrow 00:20:38.275$ and me had been studying fit in relation

NOTE Confidence: 0.937294331428571

 $00:20:38.275 \rightarrow 00:20:40.765$ to Alzheimer's and alcohol use disorders.

NOTE Confidence: 0.937294331428571

 $00{:}20{:}40.770 \dashrightarrow 00{:}20{:}42.906$ For me, even though we had been getting

NOTE Confidence: 0.937294331428571

 $00{:}20{:}42.906 \dashrightarrow 00{:}20{:}45.595$ more and more interested in the postsynaptic

NOTE Confidence: 0.937294331428571

 $00{:}20{:}45.595 \dashrightarrow 00{:}20{:}47.685$ density in the gluta matergic signaling.

NOTE Confidence: 0.937294331428571

 $00{:}20{:}47.690 \dashrightarrow 00{:}20{:}50.290$ Based on our postmortem results,

 $00:20:50.290 \rightarrow 00:20:52.264$ 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

 $00:20:54.730 \longrightarrow 00:20:56.650$ and it is a member of this group.

NOTE Confidence: 0.937294331428571

 $00:20:56.650 \rightarrow 00:20:59.575$ Detergent, postsynaptic density and it

NOTE Confidence: 0.937294331428571

 $00:20:59.575 \rightarrow 00:21:01.915$ regulates the cytoarchitecture dynamics.

NOTE Confidence: 0.937294331428571

 $00{:}21{:}01{.}920 \dashrightarrow 00{:}21{:}04{.}080$ 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

 $00:21:06.960 \rightarrow 00:21:08.640$ using machine learning strategies,

NOTE Confidence: 0.937294331428571

 $00{:}21{:}08.640 \dashrightarrow 00{:}21{:}10.232$ and I'll come to that a little later

NOTE Confidence: 0.937294331428571

 $00:21:10.232 \longrightarrow 00:21:11.738$ in the orbital frontal cortex.

NOTE Confidence: 0.937294331428571

 $00:21:11.740 \rightarrow 00:21:14.362$ Another brain region critical in substance

NOTE Confidence: 0.937294331428571

 $00:21:14.362 \longrightarrow 00:21:17.196$ 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

 $00:21:21.360 \longrightarrow 00:21:23.260$ So in looking at Finn,

NOTE Confidence: 0.937294331428571

 $00:21:23.260 \rightarrow 00:21:26.196$ 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
- $00{:}21{:}26{.}930 \dashrightarrow 00{:}21{:}29{.}122$ We also saw it on the gene expression
- NOTE Confidence: 0.937294331428571
- $00:21:29.122 \longrightarrow 00:21:30.689$ level in in the striatum.
- NOTE Confidence: 0.937294331428571
- $00{:}21{:}30.690 \dashrightarrow 00{:}21{:}33.056$ We saw it also change in animals
- NOTE Confidence: 0.937294331428571
- $00{:}21{:}33.056 \dashrightarrow 00{:}21{:}34.774$ that self administered heroin and
- NOTE Confidence: 0.937294331428571
- $00{:}21{:}34{.}774 \dashrightarrow 00{:}21{:}36{.}886$ 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
- $00:21:38.410 \rightarrow 00:21:40.160$ It correlated with their harrowing
- NOTE Confidence: 0.937294331428571
- $00{:}21{:}40.160 \dashrightarrow 00{:}21{:}42.286$ intake because here and at least
- NOTE Confidence: 0.937294331428571
- $00:21:42.286 \rightarrow 00:21:44.491$ the animals we know exactly how much
- NOTE Confidence: 0.937294331428571
- $00:21:44.491 \rightarrow 00:21:46.447$ hearing they take over their lives.
- NOTE Confidence: 0.937294331428571
- $00:21:46.450 \longrightarrow 00:21:49.817$ We also saw it in cell cultures
- NOTE Confidence: 0.937294331428571
- $00{:}21{:}49{.}817 \dashrightarrow 00{:}21{:}51{.}260$ in with morphine.
- NOTE Confidence: 0.937294331428571
- $00{:}21{:}51{.}260 \dashrightarrow 00{:}21{:}53{.}090$ So.
- NOTE Confidence: 0.937294331428571
- $00:21:53.090 \rightarrow 00:21:54.990$ Thin as a kinase,
- NOTE Confidence: 0.937294331428571

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

NOTE Confidence: 0.937294331428571

 $00{:}21{:}56.890 \dashrightarrow 00{:}21{:}58.883$ downstream signaling relates to

NOTE Confidence: 0.937294331428571

 $00{:}21{:}58{.}883 \dashrightarrow 00{:}22{:}01{.}293$ it being an phosphorylated and

NOTE Confidence: 0.937294331428571

 $00:22:01.293 \rightarrow 00:22:03.180$ its phosphorylated active form.

NOTE Confidence: 0.937294331428571

 $00:22:03.180 \longrightarrow 00:22:06.284$ Inherent users was significantly

NOTE Confidence: 0.937294331428571

 $00{:}22{:}06{.}284 \dashrightarrow 00{:}22{:}08{.}352$ increased as compared to the

NOTE Confidence: 0.937294331428571

 $00{:}22{:}08{.}352 \dashrightarrow 00{:}22{:}09{.}967$ inactive form of first decreased.

NOTE Confidence: 0.937294331428571

 $00{:}22{:}09{.}970 \dashrightarrow 00{:}22{:}11{.}990$ And indeed spin correlated with

NOTE Confidence: 0.937294331428571

 $00{:}22{:}11.990 \dashrightarrow 00{:}22{:}14.819$ the years of heroin use in humans.

NOTE Confidence: 0.937294331428571

 $00:22:14.820 \longrightarrow 00:22:15.934$ So altogether,

NOTE Confidence: 0.937294331428571

 $00:22:15.934 \rightarrow 00:22:21.610$ Finn was became very interesting for us and.

NOTE Confidence: 0.937294331428571

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

NOTE Confidence: 0.937294331428571

 $00:22:25.290 \rightarrow 00:22:28.146$ including you know a lot of the colleagues,

NOTE Confidence: 0.937294331428571

 $00{:}22{:}28.150 \dashrightarrow 00{:}22{:}30.580$ your colleagues you know had shown

NOTE Confidence: 0.937294331428571

 $00:22:30.580 \longrightarrow 00:22:33.352$ Finn related to aspects of Alzheimer's

NOTE Confidence: 0.937294331428571

 $00:22:33.352 \rightarrow 00:22:36.042$ because Finn phosphorylates the important

- NOTE Confidence: 0.937294331428571
- $00{:}22{:}36.042 \dashrightarrow 00{:}22{:}38.568$ downstream target of Finn is Tau,
- NOTE Confidence: 0.937294331428571
- $00{:}22{:}38.570 \dashrightarrow 00{:}22{:}41.000$ and hyperphosphorylated Tau is a
- NOTE Confidence: 0.937294331428571
- 00:22:41.000 --> 00:22:42.944 pathological feature of Alzheimer's
- NOTE Confidence: 0.937294331428571
- $00:22:42.944 \rightarrow 00:22:45.644$ and another among other tauopathies,
- NOTE Confidence: 0.937294331428571
- $00:22:45.644 \rightarrow 00:22:48.206$ these neurodegenerative disorders.
- NOTE Confidence: 0.937294331428571
- $00{:}22{:}48.206 \dashrightarrow 00{:}22{:}50.920$ And years before we had seen
- NOTE Confidence: 0.937294331428571
- $00:22:50.920 \longrightarrow 00:22:52.036$ these epigenetic changes,
- NOTE Confidence: 0.937294331428571
- $00:22:52.040 \rightarrow 00:22:54.926$ we had actually seen increase phosphorylate.
- NOTE Confidence: 0.937294331428571
- $00{:}22{:}54{.}930 \dashrightarrow 00{:}22{:}56{.}340$ Towel in the brains of heroin.
- NOTE Confidence: 0.937294331428571
- $00:22:56.340 \rightarrow 00:23:00.360$ Users in streaming, especially in Cortex.
- NOTE Confidence: 0.937294331428571
- 00:23:00.360 --> 00:23:03.300 So the question is, you know,
- NOTE Confidence: 0.937294331428571
- $00:23:03.300 \rightarrow 00:23:05.226$ can you see the same things in animal models?
- NOTE Confidence: 0.937294331428571
- $00:23:05.230 \longrightarrow 00:23:06.166$ So because humans,
- NOTE Confidence: 0.937294331428571
- $00{:}23{:}06{.}166 \dashrightarrow 00{:}23{:}08{.}743$ and especially I'd said at the time when
- NOTE Confidence: 0.937294331428571
- $00{:}23{:}08{.}743 \dashrightarrow 00{:}23{:}10{.}717$ we had found the increased phosphorylated
- NOTE Confidence: 0.937294331428571

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

NOTE Confidence: 0.937294331428571

 $00:23:13.363 \rightarrow 00:23:15.353$ before we started studying epigenetics,

NOTE Confidence: 0.937294331428571

 $00{:}23{:}15{.}360 \dashrightarrow 00{:}23{:}17{.}205$ I thought that they had just hit their hats

NOTE Confidence: 0.937294331428571

 $00:23:17.205 \rightarrow 00:23:18.737$ because you know when they're toxicated,

NOTE Confidence: 0.727810328181818

 $00:23:18.740 \longrightarrow 00:23:20.284$ maybe they had fallen.

NOTE Confidence: 0.727810328181818

 $00{:}23{:}20{.}284 \dashrightarrow 00{:}23{:}23{.}120$ But we when animals self administered heroin,

NOTE Confidence: 0.727810328181818

 $00:23:23.120 \rightarrow 00:23:26.240$ 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

 $00{:}23{:}27{.}960 \dashrightarrow 00{:}23{:}30{.}540$ Tau that we could also replicate.

NOTE Confidence: 0.727810328181818

 $00{:}23{:}30{.}540 \dashrightarrow 00{:}23{:}33{.}347$ You are in our cell culture model.

NOTE Confidence: 0.727810328181818

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

NOTE Confidence: 0.727810328181818

 $00{:}23{:}33{.}970 \dashrightarrow 00{:}23{:}36{.}450$ thin phosphorylated Tau phosphorylates

NOTE Confidence: 0.727810328181818

 $00{:}23{:}36{.}450 \dashrightarrow 00{:}23{:}39{.}950$ toward a specific sites on Tau,

NOTE Confidence: 0.727810328181818

 $00{:}23{:}39{.}950 \dashrightarrow 00{:}23{:}42{.}821$ and when you look at other sites that are

NOTE Confidence: 0.727810328181818

 $00:23:42.821 \rightarrow 00:23:44.628$ phosphorylated by other kinases and Tau,

NOTE Confidence: 0.727810328181818

 $00:23:44.630 \longrightarrow 00:23:46.190$ we did not see those changes,

- NOTE Confidence: 0.727810328181818
- $00{:}23{:}46.190 \dashrightarrow 00{:}23{:}48.760$ so there was for Tau.
- NOTE Confidence: 0.727810328181818
- $00:23:48.760 \rightarrow 00:23:51.392$ There were five specific changes in regard
- NOTE Confidence: 0.727810328181818
- $00:23:51.392 \rightarrow 00:23:53.340$ to its phosphorylation and function.
- NOTE Confidence: 0.8638507
- $00:23:55.650 \rightarrow 00:23:59.616$ 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
- $00:24:02.644 \rightarrow 00:24:04.312$ 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
- $00{:}24{:}06{.}924 \dashrightarrow 00{:}24{:}09{.}030$ We see these changes in regard
- NOTE Confidence: 0.8638507
- $00{:}24{:}09{.}106 \dashrightarrow 00{:}24{:}11{.}041$ now to these epigenetic changes
- NOTE Confidence: 0.8638507
- $00:24:11.041 \longrightarrow 00:24:13.839$ that really is not due to hitting.
- NOTE Confidence: 0.8638507
- $00{:}24{:}13.840 \dashrightarrow 00{:}24{:}16.258$ You know people hitting their heads
- NOTE Confidence: 0.8638507
- $00{:}24{:}16{.}258 \dashrightarrow 00{:}24{:}18{.}817$ or you know taking other substances NOTE Confidence: 0.8638507
- $00:24:18.817 \rightarrow 00:24:21.146$ but might be very, you know,
- NOTE Confidence: 0.8638507
- $00{:}24{:}21{.}146 \dashrightarrow 00{:}24{:}23{.}197$ 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

 $00:24:25.300 \rightarrow 00:24:27.820$ 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

 $00:24:29.672 \longrightarrow 00:24:31.987$ and so my student Brandy.

NOTE Confidence: 0.8638507

 $00:24:31.990 \longrightarrow 00:24:33.244$ We've been looking at this in

NOTE Confidence: 0.8638507

 $00:24:33.244 \rightarrow 00:24:34.765$ a number of ways and I'm only

NOTE Confidence: 0.8638507

 $00{:}24{:}34{.}765 \dashrightarrow 00{:}24{:}36{.}037$ going to show like one thing.

NOTE Confidence: 0.8638507

 $00{:}24{:}36{.}040 \dashrightarrow 00{:}24{:}39{.}764$ So if we look at electronic health

NOTE Confidence: 0.8638507

 $00:24:39.764 \rightarrow 00:24:43.109$ records and track opioid exposure.

NOTE Confidence: 0.8638507

 $00{:}24{:}43.110 \dashrightarrow 00{:}24{:}46.379$ And your cognitive diagnosis later in life.

NOTE Confidence: 0.8638507

 $00:24:46.380 \longrightarrow 00:24:47.994$ Indeed, we actually see that if

NOTE Confidence: 0.8638507

 $00{:}24{:}47{.}994 \dashrightarrow 00{:}24{:}50{.}098$ 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

 $00{:}24{:}51{.}550 \dashrightarrow 00{:}24{:}54{.}091$ we can talk about it and the

NOTE Confidence: 0.8638507

 $00{:}24{:}54.091 \dashrightarrow 00{:}24{:}55.686$ Q eight time period.

NOTE Confidence: 0.8638507

 $00{:}24{:}55{.}686 \dashrightarrow 00{:}24{:}57{.}851$ But in looking at retrospectively

NOTE Confidence: 0.8638507

 $00:24:57.851 \rightarrow 00:25:01.002$ and looking at 5 and 10 year

- NOTE Confidence: 0.8638507
- $00{:}25{:}01.002 \dashrightarrow 00{:}25{:}02.778$ follow-up following opioid exposure,

 $00:25:02.780 \longrightarrow 00:25:05.405$ 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

 $00:25:07.400 \longrightarrow 00:25:09.600$ especially opiate use disorder.

NOTE Confidence: 0.8638507

 $00:25:09.600 \longrightarrow 00:25:11.800$ It increased their diagnosis

NOTE Confidence: 0.8638507

 $00:25:11.800 \longrightarrow 00:25:13.698$ for neurocognitive their

NOTE Confidence: 0.8638507

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

NOTE Confidence: 0.8638507

 $00:25:15.140 \longrightarrow 00:25:17.380$ Later on in life.

NOTE Confidence: 0.8638507

 $00{:}25{:}17.380 \dashrightarrow 00{:}25{:}21.516$ So, but back to our final story so.

NOTE Confidence: 0.8638507

 $00:25:21.520 \rightarrow 00:25:23.998$ In animals, such self administered heroin,

NOTE Confidence: 0.8638507

 $00:25:24.000 \rightarrow 00:25:25.540$ just like our heroin users.

NOTE Confidence: 0.8638507

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

NOTE Confidence: 0.8638507

 $00{:}25{:}26.359 \dashrightarrow 00{:}25{:}28.270$ we saw this increase in Finn and

NOTE Confidence: 0.8638507

 $00{:}25{:}28{.}339 \dashrightarrow 00{:}25{:}30{.}383$ it made us interested to think of

NOTE Confidence: 0.8638507

 $00:25:30.383 \rightarrow 00:25:32.657$ whether or not Finn may be important,

 $00:25:32.660 \rightarrow 00:25:34.970$ for indeed directly causally regulating

NOTE Confidence: 0.8638507

 $00{:}25{:}34{.}970 \dashrightarrow 00{:}25{:}36{.}818$ heroin self administration behavior.

NOTE Confidence: 0.8638507

 $00:25:36.820 \rightarrow 00:25:37.388$ So we,

NOTE Confidence: 0.8638507

 $00{:}25{:}37{.}388 \dashrightarrow 00{:}25{:}39{.}092$ we changed the expression of Finn

NOTE Confidence: 0.8638507

 $00{:}25{:}39{.}092 \dashrightarrow 00{:}25{:}41{.}230$ by using viral media to minute

NOTE Confidence: 0.8638507

 $00{:}25{:}41{.}230 \dashrightarrow 00{:}25{:}42{.}738$ manipulations and the animals,

NOTE Confidence: 0.8638507

 $00:25:42.740 \longrightarrow 00:25:44.096$ 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

 $00{:}25{:}45{.}540 \dashrightarrow 00{:}25{:}48{.}320$ you could actually reduce heroin

NOTE Confidence: 0.8638507

 $00:25:48.320 \dashrightarrow 00:25:51.100$ 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

 $00:25:54.352 \rightarrow 00:25:55.978$ is medication development,

NOTE Confidence: 0.8638507

 $00{:}25{:}55{.}980 \dashrightarrow 00{:}25{:}58{.}234$ we wanted to see whether or not

NOTE Confidence: 0.8638507

 $00{:}25{:}58{.}234 \dashrightarrow 00{:}25{:}59{.}200$ a pharmacological inhibition

NOTE Confidence: 0.8638507

 $00:25:59.262 \longrightarrow 00:26:00.497$ of fan could also work,

NOTE Confidence: 0.8638507

 $00:26:00.500 \rightarrow 00:26:04.683$ and there now this time we are lucky

- NOTE Confidence: 0.8638507
- $00:26:04.683 \rightarrow 00:26:06.969$ because then there was a inhibitor

 $00:26:06.969 \rightarrow 00:26:09.620$ 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

 $00{:}26{:}11{.}380 \dashrightarrow 00{:}26{:}13{.}468$ and so we could use it in our animal

NOTE Confidence: 0.8638507

 $00{:}26{:}13.468 \dashrightarrow 00{:}26{:}15.322$ models and we really made sure

NOTE Confidence: 0.8638507

 $00:26:15.322 \rightarrow 00:26:16.887$ that animals were quite motivated.

NOTE Confidence: 0.8638507

 $00:26:16.890 \longrightarrow 00:26:18.906$ We increased increasing the work effort

NOTE Confidence: 0.8638507

 $00{:}26{:}18.906 \dashrightarrow 00{:}26{:}21.390$ for them to self administer heroin.

NOTE Confidence: 0.8638507

 $00{:}26{:}21{.}390 \dashrightarrow 00{:}26{:}22{.}930$ And then gave them sarcasm.

NOTE Confidence: 0.8638507

 $00:26:22.930 \longrightarrow 00:26:24.340$ And during those days that

NOTE Confidence: 0.8638507

 $00:26:24.340 \longrightarrow 00:26:25.468$ they have received sarcastic,

NOTE Confidence: 0.8638507

 $00{:}26{:}25{.}470 \dashrightarrow 00{:}26{:}28{.}506$ it had reduced their currency and

NOTE Confidence: 0.8638507

 $00{:}26{:}28{.}506 \dashrightarrow 00{:}26{:}30{.}024$ self administration behavior.

NOTE Confidence: 0.8638507

 $00:26:30.030 \longrightarrow 00:26:32.322$ In your when you're trying to

NOTE Confidence: 0.8638507

 $00{:}26{:}32{.}322 \dashrightarrow 00{:}26{:}33{.}850$ develop medications for substance

 $00:26:33.916 \rightarrow 00:26:35.916$ use disorders is really critical.

NOTE Confidence: 0.8638507

 $00{:}26{:}35{.}920 \dashrightarrow 00{:}26{:}38{.}662$ 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

 $00:26:40.666 \rightarrow 00:26:43.200$ 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

 $00{:}26{:}44{.}360 \dashrightarrow 00{:}26{:}46{.}425$ And when we gave a sarcastic name

NOTE Confidence: 0.8638507

 $00:26:46.425 \rightarrow 00:26:48.500$ while their self administering food,

NOTE Confidence: 0.8638507

 $00:26:48.500 \rightarrow 00:26:51.909$ for example, it didn't change that behavior.

NOTE Confidence: 0.8638507

 $00{:}26{:}51{.}910 \dashrightarrow 00{:}26{:}54{.}286$ So when we look at the the human brain

NOTE Confidence: 0.8638507

 $00{:}26{:}54{.}286 \dashrightarrow 00{:}26{:}56{.}628$ and our translational animal models,

NOTE Confidence: 0.8638507

 $00{:}26{:}56{.}630 \dashrightarrow 00{:}26{:}59{.}096$ 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

 $00:27:00.740 \longrightarrow 00:27:02.970$ 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
- $00:27:07.819 \longrightarrow 00:27:09.875$ have identified may be important

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

NOTE Confidence: 0.924738736

 $00:27:11.380 \longrightarrow 00:27:13.440$ But just as the epigenetic,

NOTE Confidence: 0.924738736

 $00:27:13.440 \longrightarrow 00:27:16.221$ the BRD the Bromo domain family that we

NOTE Confidence: 0.924738736

 $00:27:16.221 \rightarrow 00:27:19.057$ think is important for developing medication,

NOTE Confidence: 0.924738736

 $00{:}27{:}19.060 \dashrightarrow 00{:}27{:}21.596$ others have and we saw and they saw

NOTE Confidence: 0.924738736

 $00:27:21.596 \rightarrow 00:27:23.209$ other substances being impacted.

NOTE Confidence: 0.924738736

 $00:27:23.210 \longrightarrow 00:27:26.201$ 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

 $00{:}27{:}29{.}729 \dashrightarrow 00{:}27{:}33{.}021$ dorid Bronze group at UCSF was able to see NOTE Confidence: 0.924738736

 $00:27:33.021 \rightarrow 00:27:36.480$ 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

 $00{:}27{:}39{.}304 \dashrightarrow 00{:}27{:}42{.}758$ if they use their cabinet it could decrease

NOTE Confidence: 0.924738736

 $00{:}27{:}42.758 \dashrightarrow 00{:}27{:}45.270$ the animals alcohol intake behavior.

NOTE Confidence: 0.924738736

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

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

 $00:27:52.450 \longrightarrow 00:27:53.692$ alcohol use disorder,

NOTE Confidence: 0.924738736

 $00:27:53.692 \rightarrow 00:27:56.176$ and have not seen any significant

NOTE Confidence: 0.924738736

 $00{:}27{:}56.176 \dashrightarrow 00{:}27{:}58.308$ 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

 $00{:}28{:}01{.}636 \dashrightarrow 00{:}28{:}03{.}267$ also had a mouse model where they

NOTE Confidence: 0.924738736

 $00{:}28{:}03{.}320 \dashrightarrow 00{:}28{:}05{.}498$ could see that perhaps perhaps the NOTE Confidence: 0.924738736

 $00:28:05.498 \rightarrow 00:28:08.268$ habitual responded for for ethanol,

NOTE Confidence: 0.924738736

 $00:28:08.270 \longrightarrow 00:28:10.700$ maybe what may be affected by

NOTE Confidence: 0.924738736

 $00{:}28{:}10.700 \dashrightarrow 00{:}28{:}13.208$ our cabinet and there's and those

NOTE Confidence: 0.924738736

 $00:28:13.208 \longrightarrow 00:28:15.228$ of course may be important.

NOTE Confidence: 0.924738736

 $00:28:15.230 \rightarrow 00:28:18.266$ So here we did not see, at least for alcohol.

NOTE Confidence: 0.924738736

 $00:28:18.266 \longrightarrow 00:28:20.630$ Just sort of carry that by.

NOTE Confidence: 0.924738736

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

 $00{:}28{:}22{.}202 \dashrightarrow 00{:}28{:}24{.}298$ that circadian pattern effect?

NOTE Confidence: 0.924738736

 $00:28:24.300 \longrightarrow 00:28:26.351$ 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

 $00{:}28{:}28{.}391 \dashrightarrow 00{:}28{:}30{.}701$ 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

 $00{:}28{:}33{.}520 \dashrightarrow 00{:}28{:}36{.}238$ least opiate use changes that we saw.

NOTE Confidence: 0.924738736

 $00{:}28{:}36{.}240 \dashrightarrow 00{:}28{:}38{.}704$ So I'm gonna go back to the orbital

NOTE Confidence: 0.924738736

 $00:28:38.704 \rightarrow 00:28:40.596$ frontal cortex where if you remember

NOTE Confidence: 0.924738736

 $00{:}28{:}40.596 \dashrightarrow 00{:}28{:}42.660$ we had seen this changes in fan

NOTE Confidence: 0.924738736

 $00{:}28{:}42.660 \dashrightarrow 00{:}28{:}43.980$ 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

 $00{:}28{:}45{.}244 \dashrightarrow 00{:}28{:}47{.}140$ is is a critical brain region

NOTE Confidence: 0.924738736

 $00{:}28{:}47{.}210 \dashrightarrow 00{:}28{:}49{.}320$ also for substance use disorder,

NOTE Confidence: 0.924738736

 $00{:}28{:}49{.}320 \dashrightarrow 00{:}28{:}51{.}905$ especially in terms of guiding

NOTE Confidence: 0.924738736

 $00:28:51.905 \rightarrow 00:28:52.939$ decision making.

 $00:28:52.940 \longrightarrow 00:28:54.628$ The values of reward,

NOTE Confidence: 0.924738736

 $00{:}28{:}54.628 \dashrightarrow 00{:}28{:}56.738$ goal directed behavior and even

NOTE Confidence: 0.924738736

 $00:28:56.738 \rightarrow 00:28:59.430$ 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

 $00{:}29{:}03{.}310 \dashrightarrow 00{:}29{:}06{.}130$ Significantly changed gene hub

NOTE Confidence: 0.924738736

 $00:29:06.130 \rightarrow 00:29:08.950$ using machine learning approaches.

NOTE Confidence: 0.924738736

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

NOTE Confidence: 0.924738736

 $00{:}29{:}12{.}720 \dashrightarrow 00{:}29{:}15{.}750$ 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

 $00{:}29{:}18.655 \dashrightarrow 00{:}29{:}21.078$ machine learning models predicted

NOTE Confidence: 0.924738736

 $00{:}29{:}21.080 \dashrightarrow 00{:}29{:}24.278$ 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

 $00:29:27.940 \rightarrow 00:29:30.772$ Differentiating the gene expression

NOTE Confidence: 0.924738736

 $00:29:30.772 \longrightarrow 00:29:33.340$ pattern of parent users from control.

NOTE Confidence: 0.924738736

 $00:29:33.340 \longrightarrow 00:29:35.158$ 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
- $00:29:37.840 \longrightarrow 00:29:41.326$ how? How well do these these?
- NOTE Confidence: 0.924738736
- $00:29:41.330 \longrightarrow 00:29:44.666$ Transcriptional signatures tell you who's a.
- NOTE Confidence: 0.924738736
- $00:29:44.670 \longrightarrow 00:29:47.162$ Maybe a heroin user and who is
- NOTE Confidence: 0.924738736
- $00{:}29{:}47.162 \dashrightarrow 00{:}29{:}48.230$ a control subject.
- NOTE Confidence: 0.924738736
- $00:29:48.230 \longrightarrow 00:29:49.230$ And as I said,
- NOTE Confidence: 0.924738736
- $00:29:49.230 \longrightarrow 00:29:51.150$ she's a 17 up all the time,
- NOTE Confidence: 0.924738736
- $00:29:51.150 \longrightarrow 00:29:53.690$ 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
- $00:29:56.810 \longrightarrow 00:29:58.890$ subunit and the the.
- NOTE Confidence: 0.924738736
- $00{:}29{:}58.890 \dashrightarrow 00{:}30{:}00.708$ Unfortunate thing is that actually a
- NOTE Confidence: 0.924738736
- $00{:}30{:}00{.}708 \dashrightarrow 00{:}30{:}02{.}989$ good thing and an unfortunate thing.
- NOTE Confidence: 0.924738736
- $00:30:02.990 \longrightarrow 00:30:05.231$ The good thing is that for us is that
- NOTE Confidence: 0.924738736
- $00:30:05.231 \rightarrow 00:30:07.270$ it's something novel because very,
- NOTE Confidence: 0.924738736
- $00:30:07.270 \longrightarrow 00:30:10.287$ 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

 $00{:}30{:}12.650 \dashrightarrow 00{:}30{:}14.690$ not only at the Ampang

NOTE Confidence: 0.924738736

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

NOTE Confidence: 0.924738736

 $00{:}30{:}15{.}510 \dashrightarrow 00{:}30{:}18{.}422$ but even at the GABA a receptor

NOTE Confidence: 0.924738736

 $00{:}30{:}18.422 \dashrightarrow 00{:}30{:}19.670$ and different researchers

NOTE Confidence: 0.924738736

 $00{:}30{:}19.745 \dashrightarrow 00{:}30{:}21.790$ have evidence on both sides,

NOTE Confidence: 0.924738736

 $00{:}30{:}21.790 \dashrightarrow 00{:}30{:}24.758$ so that's why we are working with the

NOTE Confidence: 0.924738736

 $00{:}30{:}24.758 \dashrightarrow 00{:}30{:}27.222$ Yale your proteomics core and being

NOTE Confidence: 0.924738736

 $00:30:27.222 \rightarrow 00:30:30.560$ able to see where is Jesus 7 binding,

NOTE Confidence: 0.924738736

 $00:30:30.560 \longrightarrow 00:30:32.210$ at least in our models,

NOTE Confidence: 0.924738736

 $00:30:32.210 \longrightarrow 00:30:33.905$ 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

 $00:30:35.671 \longrightarrow 00:30:37.194$ for that, but in the meantime,

NOTE Confidence: 0.906192348333333

 $00:30:37.194 \longrightarrow 00:30:38.857$ what we've done is to try to

NOTE Confidence: 0.906192348333333

 $00:30:38.857 \rightarrow 00:30:40.547$ see is sheets of seven, really.

NOTE Confidence: 0.906192348333333

 $00:30:40.547 \rightarrow 00:30:42.338$ Critical for parents,

- NOTE Confidence: 0.906192348333333
- $00:30:42.338 \longrightarrow 00:30:45.323$ 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
- $00:30:49.470 \longrightarrow 00:30:51.648$ You could see that indeed it
- NOTE Confidence: 0.906192348333333
- $00:30:51.648 \longrightarrow 00:30:53.808$ replicated that her she's a 70
- NOTE Confidence: 0.906192348333333
- $00{:}30{:}53.808 \dashrightarrow 00{:}30{:}55.704$ and the cohorts of heroin users
- NOTE Confidence: 0.906192348333333
- $00:30:55.704 \rightarrow 00:30:57.690$ 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
- $00:30:59.694 \rightarrow 00:31:02.199$ significantly with the the the
- NOTE Confidence: 0.906192348333333
- $00:31:02.199 \rightarrow 00:31:04.719$ rest heroin seeking behavior.
- NOTE Confidence: 0.906192348333333
- $00:31:04.720 \longrightarrow 00:31:08.136$ So we could we wanted to see if
- NOTE Confidence: 0.906192348333333
- $00:31:08.136 \rightarrow 00:31:10.876$ overexpressing she's a seven could change
- NOTE Confidence: 0.906192348333333
- $00:31:10.876 \rightarrow 00:31:13.582$ was relevant to Q induced behavior
- NOTE Confidence: 0.906192348333333
- $00{:}31{:}13.670 \dashrightarrow 00{:}31{:}16.376$ so we had animals self administer
- NOTE Confidence: 0.906192348333333
- $00{:}31{:}16{.}380 \dashrightarrow 00{:}31{:}19{.}686$ heroin and also saline as comparison
- NOTE Confidence: 0.906192348333333

 $00:31:19.686 \rightarrow 00:31:21.408$ 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

 $00:31:25.456 \rightarrow 00:31:27.619$ had heroin and she's the seven we can

NOTE Confidence: 0.906192348333333

 $00:31:27.619 \longrightarrow 00:31:29.416$ 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

 $00:31:35.984 \longrightarrow 00:31:37.824$ the orbital frontal cortex is

NOTE Confidence: 0.906192348333333

 $00:31:37.824 \rightarrow 00:31:39.809$ important for reversal learning and

NOTE Confidence: 0.906192348333333

 $00{:}31{:}39{.}809 \dashrightarrow 00{:}31{:}42{.}179$ indeed over expressing she's a 7 in.

NOTE Confidence: 0.906192348333333

 $00:31:42.180 \longrightarrow 00:31:44.432$ Also change sucrose reversal

NOTE Confidence: 0.906192348333333

 $00:31:44.432 \longrightarrow 00:31:47.247$ 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

 $00:31:49.780 \longrightarrow 00:31:51.380$ we would switch and give

NOTE Confidence: 0.906192348333333

 $00:31:51.380 \longrightarrow 00:31:52.660$ them a different reward.

- NOTE Confidence: 0.906192348333333
- $00:31:52.660 \rightarrow 00:31:54.352$ They're the conditions under which the
- NOTE Confidence: 0.906192348333333
- $00{:}31{:}54{.}352 \dashrightarrow 00{:}31{:}56{.}408$ levers and we could see that it was a.
- NOTE Confidence: 0.906192348333333
- $00{:}31{:}56{.}410 \dashrightarrow 00{:}31{:}58{.}720$ She's a 7 over expression could
- NOTE Confidence: 0.906192348333333
- $00:31:58.720 \rightarrow 00:32:00.568$ promote reversal learning more
- NOTE Confidence: 0.906192348333333
- $00{:}32{:}00{.}568 \dashrightarrow 00{:}32{:}02{.}400$ versus the heroin animals.
- NOTE Confidence: 0.906192348333333
- $00:32:02.400 \rightarrow 00:32:04.976$ So the question is what is happening?
- NOTE Confidence: 0.906192348333333
- $00:32:04.980 \longrightarrow 00:32:07.976$ In the brain, on a transcriptional level.
- NOTE Confidence: 0.906192348333333
- $00:32:07.980 \longrightarrow 00:32:09.456$ With she's a 7.
- NOTE Confidence: 0.906192348333333
- $00{:}32{:}09{.}456 \dashrightarrow 00{:}32{:}12{.}805$ 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
- $00:32:19.814 \longrightarrow 00:32:21.710$ conditions of no heroin,
- NOTE Confidence: 0.906192348333333
- 00:32:21.710 --> 00:32:22.552 self administration.
- NOTE Confidence: 0.906192348333333
- $00{:}32{:}22{.}552 \dashrightarrow 00{:}32{:}25{.}078$ Just she's a 7 over expression of
- NOTE Confidence: 0.906192348333333

 $00:32:25.078 \dashrightarrow 00:32:27.039$ the orbital frontal cortex and

NOTE Confidence: 0.906192348333333

 $00{:}32{:}27.039 \dashrightarrow 00{:}32{:}29.489$ 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

 $00:32:31.770 \longrightarrow 00:32:35.190$ In comparing 2 gene expression sets,

NOTE Confidence: 0.906192348333333

 $00{:}32{:}35{.}190 \dashrightarrow 00{:}32{:}36{.}614$ it's a little convoluted.

NOTE Confidence: 0.906192348333333

00:32:36.614 --> 00:32:37.326 It's not,

NOTE Confidence: 0.906192348333333

 $00:32:37.330 \longrightarrow 00:32:39.283$ I mean that it's just the opposite

NOTE Confidence: 0.906192348333333

 $00:32:39.283 \longrightarrow 00:32:40.120$ in terms of.

NOTE Confidence: 0.906192348333333

 $00:32:40.120 \longrightarrow 00:32:43.275$ 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

 $00:32:46.529 \longrightarrow 00:32:48.857$ in one comparison group.

NOTE Confidence: 0.906192348333333

 $00{:}32{:}48.860 \dashrightarrow 00{:}32{:}50.786$ And over here these are genes

NOTE Confidence: 0.906192348333333

 $00:32:50.786 \longrightarrow 00:32:51.749$ that are upregulated,

NOTE Confidence: 0.906192348333333

 $00{:}32{:}51{.}750 \dashrightarrow 00{:}32{:}54{.}264$ but there was a complete concordance

NOTE Confidence: 0.906192348333333

 $00{:}32{:}54{.}264 \dashrightarrow 00{:}32{:}56{.}902$ between whether or not complete a

NOTE Confidence: 0.906192348333333

 $00:32:56.902 \rightarrow 00:32:59.107$ very strong concordance between the

- NOTE Confidence: 0.906192348333333
- $00:32:59.107 \rightarrow 00:33:01.904$ gene genes that are upregulated in
- NOTE Confidence: 0.906192348333333
- $00:33:01.904 \rightarrow 00:33:03.908$ hiring users and those that are
- NOTE Confidence: 0.906192348333333
- $00:33:03.908 \rightarrow 00:33:06.241$ are also upregulated by she's a 7
- NOTE Confidence: 0.906192348333333
- $00:33:06.241 \rightarrow 00:33:07.826$ overexpression and the same thing.
- NOTE Confidence: 0.906192348333333
- $00:33:07.830 \rightarrow 00:33:09.930$ Those that are downregulated so there.
- NOTE Confidence: 0.906192348333333
- $00:33:09.930 \longrightarrow 00:33:11.154$ This there is this.
- NOTE Confidence: 0.906192348333333
- 00:33:11.154 --> 00:33:12.990 She's a 7 over
expression mimics a $\ensuremath{\mathsf{7}}$
- NOTE Confidence: 0.906192348333333
- 00:33:13.055 --> 00:33:15.319 lot of the patterns in the in the
- NOTE Confidence: 0.906192348333333
- $00:33:15.319 \longrightarrow 00:33:17.421$ orbital frontal cortex that we see
- NOTE Confidence: 0.906192348333333
- $00:33:17.421 \rightarrow 00:33:18.893$ with parents often ministration.
- NOTE Confidence: 0.906192348333333
- $00:33:18.900 \rightarrow 00:33:22.330$ So and not in the discordant genes.
- NOTE Confidence: 0.906192348333333
- $00:33:22.330 \longrightarrow 00:33:24.360$ This is just the the odds ratio
- NOTE Confidence: 0.906192348333333
- $00:33:24.360 \longrightarrow 00:33:26.140$ and this this significance.
- NOTE Confidence: 0.906192348333333
- $00{:}33{:}26{.}140 \dashrightarrow 00{:}33{:}29{.}206$ So what are the biological features
- NOTE Confidence: 0.906192348333333
- $00:33:29.206 \rightarrow 00:33:32.829$ that are that are changed in relation
- NOTE Confidence: 0.906192348333333

 $00:33:32.829 \longrightarrow 00:33:36.140$ to the genes that are that she's

NOTE Confidence: 0.906192348333333

 $00:33:36.140 \longrightarrow 00:33:37.400$ a 7 regulates?

NOTE Confidence: 0.906192348333333

00:33:37.400 --> 00:33:39.806 Once again not surprising we see

NOTE Confidence: 0.906192348333333

00:33:39.806 --> 00:33:41.980 changes related to postsynaptic density,

NOTE Confidence: 0.906192348333333

00:33:41.980 --> 00:33:43.993 the synaptic plasticity,

NOTE Confidence: 0.906192348333333

 $00:33:43.993 \dashrightarrow 00:33:46.006$ the cytoskeletal organization.

NOTE Confidence: 0.906192348333333

 $00{:}33{:}46.010 \dashrightarrow 00{:}33{:}49.699$ Also we see a number of of

NOTE Confidence: 0.906192348333333

00:33:49.699 --> 00:33:51.730 of disorders related to,

NOTE Confidence: 0.906192348333333

00:33:51.730 --> 00:33:54.302 for example, Alzheimer's disease,

NOTE Confidence: 0.906192348333333

00:33:54.302 --> 00:33:55.588 Huntington's disease,

NOTE Confidence: 0.906192348333333

 $00:33:55.590 \rightarrow 00:33:57.468$ these neurodegenerative disorders

NOTE Confidence: 0.906192348333333

 $00:33:57.468 \dashrightarrow 00:34:00.598$ come into the gene transcriptional

NOTE Confidence: 0.906192348333333

 $00{:}34{:}00{.}598 \dashrightarrow 00{:}34{:}03{.}940$ profile that she's a seven is inducing.

NOTE Confidence: 0.91129993625

 $00{:}34{:}03{.}940 \dashrightarrow 00{:}34{:}06{.}300$ And even going back to the machine learning,

NOTE Confidence: 0.91129993625

 $00:34:06.300 \longrightarrow 00:34:07.353$ I'm not going to show a lot of it.

NOTE Confidence: 0.91129993625

 $00:34:07.360 \dashrightarrow 00:34:09.064$ We can see that other genes that have

- NOTE Confidence: 0.91129993625
- $00:34:09.064 \rightarrow 00:34:10.298$ 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
- $00:34:11.740 \rightarrow 00:34:13.854$ for example, here this product could here,
- NOTE Confidence: 0.91129993625
- $00:34:13.860 \longrightarrow 00:34:16.737$ is it also in she's a 7.
- NOTE Confidence: 0.91129993625
- $00{:}34{:}16{.}740 \dashrightarrow 00{:}34{:}18{.}828$ And when you change she's a 7 expression.
- NOTE Confidence: 0.91129993625
- $00{:}34{:}18.830 \dashrightarrow 00{:}34{:}20.979$ It also changes a number of these
- NOTE Confidence: 0.91129993625
- $00:34:20.979 \rightarrow 00:34:23.000$ genes that the machine learning
- NOTE Confidence: 0.91129993625
- $00{:}34{:}23.000 \dashrightarrow 00{:}34{:}26.766$ strategies had shown to relate to heroin
- NOTE Confidence: 0.91129993625
- $00{:}34{:}26.766 \dashrightarrow 00{:}34{:}29.730$ seeking behavior in in particular.
- NOTE Confidence: 0.91129993625
- $00:34:29.730 \longrightarrow 00:34:32.760$ So using these unbiased computational
- NOTE Confidence: 0.91129993625
- $00:34:32.760 \longrightarrow 00:34:36.330$ strategies, we were able to
- NOTE Confidence: 0.91129993625
- $00{:}34{:}36{.}330 \dashrightarrow 00{:}34{:}38{.}550$ identify molecular alterations,
- NOTE Confidence: 0.91129993625
- $00{:}34{:}38{.}550 \dashrightarrow 00{:}34{:}40{.}500$ again emphasizing synaptic
- NOTE Confidence: 0.91129993625
- $00{:}34{:}40{.}500 \dashrightarrow 00{:}34{:}43{.}750$ dys regulation and also this aspect
- NOTE Confidence: 0.91129993625
- $00:34:43.750 \rightarrow 00:34:46.869$ of heightened neurocognitive risk.
- NOTE Confidence: 0.87155301625

 $00:34:52.160 \longrightarrow 00:34:55.896$ So the last part of you know the

NOTE Confidence: 0.87155301625

 $00{:}34{:}55{.}900 \dashrightarrow 00{:}34{:}59{.}050$ 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

 $00{:}35{:}02{.}280 \dashrightarrow 00{:}35{:}05{.}498$ new treatments for opiate use disorder.

NOTE Confidence: 0.87155301625

 $00{:}35{:}05{.}498 \dashrightarrow 00{:}35{:}08{.}127$ The first strategies, as I mentioned,

NOTE Confidence: 0.87155301625

 $00{:}35{:}08{.}127 \dashrightarrow 00{:}35{:}10{.}281$ 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

 $00:35:16.922 \longrightarrow 00:35:18.870$ moving them into the clinical studies. NOTE Confidence: 0.9006337666666667

00:35:21.200 --> 00:35:25.790 What we are. Also did was using our NOTE Confidence: 0.9006337666666667

 $00:35:25.790 \dashrightarrow 00:35:28.817$ animal models in general to see what NOTE Confidence: 0.9006337666666667

 $00:35:28.817 \rightarrow 00:35:32.313$ they may help to identify and here this NOTE Confidence: 0.9006337666666667

 $00{:}35{:}32{.}313 \dashrightarrow 00{:}35{:}34{.}768$ was an unusual start because we've

NOTE Confidence: 0.9006337666666667

 $00:35:34.768 \rightarrow 00:35:36.448$ been looking at the developmental

NOTE Confidence: 0.9006337666666667

 $00:35:36.448 \rightarrow 00:35:38.438$ effects of cannabis for many years,

- NOTE Confidence: 0.9006337666666667
- $00:35:38.440 \dashrightarrow 00:35:41.344$ both from the prenatal and analysing
- NOTE Confidence: 0.9006337666666667
- $00:35:41.344 \rightarrow 00:35:45.019$ exposure and we had looked in in humans
- NOTE Confidence: 0.9006337666666667
- $00:35:45.020 \rightarrow 00:35:47.365$ in terms of fetal samples for example,
- NOTE Confidence: 0.9006337666666667
- $00{:}35{:}47{.}370 \dashrightarrow 00{:}35{:}49{.}002$ but even our animal models because
- NOTE Confidence: 0.9006337666666667
- $00{:}35{:}49.002 \dashrightarrow 00{:}35{:}50.645$ our animal models we could allow
- NOTE Confidence: 0.9006337666666667
- $00:35:50.645 \rightarrow 00:35:52.409$ them to grow into adults and really
- NOTE Confidence: 0.9006337666666667
- $00:35:52.409 \longrightarrow 00:35:54.050$ see doesn't impact on behavior.
- NOTE Confidence: 0.9006337666666667
- $00{:}35{:}54.050 \dashrightarrow 00{:}35{:}55.760$ And one behavior that we we spend a lot
- NOTE Confidence: 0.9006337666666667
- $00:35:55.760 \rightarrow 00:35:57.550$ of time looking at because initially,
- NOTE Confidence: 0.9006337666666667
- $00:35:57.550 \rightarrow 00:35:59.490$ especially with the adolescent exposure,
- NOTE Confidence: 0.9006337666666667
- $00:35:59.490 \rightarrow 00:36:02.610$ was this gateway hypothesis of cannabis
- NOTE Confidence: 0.9006337666666667
- 00:36:02.610 --> 00:36:04.866 exposure increasing addiction risk even
- NOTE Confidence: 0.9006337666666667
- $00{:}36{:}04.866 \dashrightarrow 00{:}36{:}07.470$ to other substances later in life.
- NOTE Confidence: 0.9006337666666667
- $00{:}36{:}07{.}470 \dashrightarrow 00{:}36{:}10{.}956$ And here we looked at opioids and.
- NOTE Confidence: 0.9006337666666667
- $00{:}36{:}10.960 \dashrightarrow 00{:}36{:}12.760$ And then we can go into QA as to
- NOTE Confidence: 0.9006337666666667

 $00:36:12.760 \longrightarrow 00:36:14.189$ why we looked at opioids,

NOTE Confidence: 0.9006337666666667

 $00{:}36{:}14.190 \dashrightarrow 00{:}36{:}17.030$ but there is a they share a number

NOTE Confidence: 0.9006337666666667

 $00:36:17.030 \dashrightarrow 00:36:19.825$ of signaling mechanisms with the

NOTE Confidence: 0.9006337666666667

 $00:36:19.825 \rightarrow 00:36:21.829$ endogenous cannabinoid receptors.

NOTE Confidence: 0.9006337666666667

 $00{:}36{:}21.830 \dashrightarrow 00{:}36{:}24.322$ And we could see in animals that

NOTE Confidence: 0.9006337666666667

 $00:36:24.322 \rightarrow 00:36:26.770$ had been exposed to THC prenatally,

NOTE Confidence: 0.9006337666666667

 $00:36:26.770 \dashrightarrow 00:36:29.035$ that they would self administer

NOTE Confidence: 0.9006337666666667

 $00:36:29.035 \longrightarrow 00:36:30.847$ heroin more than controls,

NOTE Confidence: 0.9006337666666667

 $00:36:30.850 \longrightarrow 00:36:32.130$ and even on their conditions,

NOTE Confidence: 0.9006337666666667

 $00:36:32.130 \longrightarrow 00:36:33.640$ when they we had them,

NOTE Confidence: 0.9006337666666667

 $00{:}36{:}33{.}640 \dashrightarrow 00{:}36{:}35{.}728$ they would take the same amount of heroin.

NOTE Confidence: 0.9006337666666667

00:36:35.730 - 00:36:38.258 If you just looked at even the first,

NOTE Confidence: 0.9006337666666667

 $00:36:38.260 \longrightarrow 00:36:40.913$ they're running to the first letter lever

NOTE Confidence: 0.9006337666666667

 $00:36:40.913 \rightarrow 00:36:43.988$ to get that first hit of of heroin.

NOTE Confidence: 0.9006337666666667

 $00:36:43.990 \dashrightarrow 00:36:46.666$ In those adult animals, with penalty, etc.

NOTE Confidence: 0.9006337666666667

 $00:36:46.666 \rightarrow 00:36:47.850$ It was much faster,

- NOTE Confidence: 0.9006337666666667
- $00:36:47.850 \rightarrow 00:36:50.370$ and they had a greater drug seeking behavior,
- NOTE Confidence: 0.9006337666666667
- 00:36:50.370 --> 00:36:52.320 especially under stressful.
- NOTE Confidence: 0.9006337666666667
- 00:36:52.320 --> 00:36:53.620 Conditions similarly,
- NOTE Confidence: 0.9006337666666667
- $00:36:53.620 \rightarrow 00:36:56.410$ when we gave adult animals have
- NOTE Confidence: 0.9006337666666667
- $00:36:56.410 \rightarrow 00:36:59.360$ had adolescent exposure to to TFC.
- NOTE Confidence: 0.9006337666666667
- $00:36:59.360 \dashrightarrow 00:37:01.980$ They also self administered this
- NOTE Confidence: 0.9006337666666667
- $00:37:01.980 \longrightarrow 00:37:03.540$ black line here that's missing.
- NOTE Confidence: 0.9006337666666667
- $00:37:03.540 \longrightarrow 00:37:06.648$ They also self administered more heroin.
- NOTE Confidence: 0.9006337666666667
- $00:37:06.650 \longrightarrow 00:37:09.080$ But when we?
- NOTE Confidence: 0.9006337666666667
- 00:37:09.080 --> 00:37:10.796 When we have our human studies,
- NOTE Confidence: 0.9006337666666667
- $00:37:10.800 \dashrightarrow 00:37:12.675$ we're talking about cannabis and
- NOTE Confidence: 0.9006337666666667
- $00{:}37{:}12.675 \dashrightarrow 00{:}37{:}15.045$ when we have our animal studies
- NOTE Confidence: 0.9006337666666667
- 00:37:15.045 00:37:16.757 we're talking about THC.
- NOTE Confidence: 0.9006337666666667
- $00{:}37{:}16.760 \dashrightarrow 00{:}37{:}18.392$ And we know that the cannabis
- NOTE Confidence: 0.9006337666666667
- $00:37:18.392 \rightarrow 00:37:19.480$ plant is very complex,
- NOTE Confidence: 0.9006337666666667

00:37:19.480 --> 00:37:21.628 containing over 500 chemicals,

NOTE Confidence: 0.9006337666666667

 $00:37:21.628 \longrightarrow 00:37:25.244$ many of them over 140, are cannabinoids.

NOTE Confidence: 0.9006337666666667

 $00:37:25.244 \rightarrow 00:37:28.660$ So THC yes is the primary psychoactive

NOTE Confidence: 0.9006337666666667

00:37:28.660 --> 00:37:30.556 cannabinoid in cannabis plant,

NOTE Confidence: 0.9006337666666667

 $00:37:30.556 \rightarrow 00:37:33.400$ but other cannabinoids such as CBD,

NOTE Confidence: 0.9006337666666667

 $00{:}37{:}33{.}400 \dashrightarrow 00{:}37{:}34{.}726$ cannabidiol is.

NOTE Confidence: 0.9006337666666667

00:37:34.726 --> 00:37:36.052 You know,

NOTE Confidence: 0.9006337666666667

 $00{:}37{:}36.052 \dashrightarrow 00{:}37{:}39.282$ also have from ecological and

NOTE Confidence: 0.9006337666666667

 $00{:}37{:}39{.}282 \dashrightarrow 00{:}37{:}41{.}818$ and and psychoactive properties,

NOTE Confidence: 0.9006337666666667

 $00:37:41.820 \longrightarrow 00:37:43.572$ so one of the things we wanted to

NOTE Confidence: 0.9006337666666667

 $00{:}37{:}43.572 \dashrightarrow 00{:}37{:}45.584$ look at was that we said let's look

NOTE Confidence: 0.9006337666666667

 $00{:}37{:}45{.}584 \dashrightarrow 00{:}37{:}47{.}290$ at at least another cannabinoid.

NOTE Confidence: 0.9006337666666667

00:37:47.290 --> 00:37:49.150 CBD, it's used to be well.

NOTE Confidence: 0.9006337666666667

 $00:37:49.150 \longrightarrow 00:37:52.054$ It still technically is the second

NOTE Confidence: 0.9006337666666667

 $00:37:52.054 \rightarrow 00:37:54.958$ highest cannabinoid in the cannabis plant.

NOTE Confidence: 0.9006337666666667

 $00:37:54.960 \rightarrow 00:37:57.067$ The you know the normal cannabis plant.

- NOTE Confidence: 0.9006337666666667
- 00:37:57.070 --> 00:37:58.834 Today it's decreased dramatically
- NOTE Confidence: 0.9006337666666667
- $00{:}37{:}58{.}834 \dashrightarrow 00{:}38{:}01{.}039$ as compared to the concentrations
- NOTE Confidence: 0.9006337666666667
- $00:38:01.039 \rightarrow 00:38:03.317$ of THC that have gotten higher.
- NOTE Confidence: 0.9006337666666667
- $00:38:03.320 \longrightarrow 00:38:05.770$ And when we looked in our animal
- NOTE Confidence: 0.9006337666666667
- $00:38:05.770 \rightarrow 00:38:08.400$ models that had been given CBD,
- NOTE Confidence: 0.9006337666666667
- $00{:}38{:}08{.}400 \dashrightarrow 00{:}38{:}09{.}672$ we saw a different pattern to
- NOTE Confidence: 0.9006337666666667
- $00:38:09.672 \rightarrow 00:38:10.760$ what we saw with THC.
- NOTE Confidence: 0.9006337666666667
- 00:38:10.760 --> 00:38:12.048 As I said earlier,
- NOTE Confidence: 0.9006337666666667
- $00{:}38{:}12.048 \dashrightarrow 00{:}38{:}13.658$ with THC animals would invariably
- NOTE Confidence: 0.9006337666666667
- 00:38:13.658 --> 00:38:15.238 self administer more heroin is
- NOTE Confidence: 0.9006337666666667
- $00:38:15.238 \rightarrow 00:38:17.651$ given to you to earlier and what we
- NOTE Confidence: 0.9006337666666667
- $00{:}38{:}17.651 \dashrightarrow 00{:}38{:}19.590$ saw with CBD was that it decreased
- NOTE Confidence: 0.9006337666666667
- $00:38:19.590 \longrightarrow 00:38:20.772$ heroin seeking behavior,
- NOTE Confidence: 0.9006337666666667
- $00{:}38{:}20.772 \dashrightarrow 00{:}38{:}23.478$ and it was very specific it
- NOTE Confidence: 0.9006337666666667
- $00{:}38{:}23.478 \dashrightarrow 00{:}38{:}25.358$ was decreasing Q and juice.
- NOTE Confidence: 0.9006337666666667

 $00:38:25.360 \rightarrow 00:38:27.075$ Currently seeking behavior so animals

NOTE Confidence: 0.9006337666666667

 $00:38:27.075 \dashrightarrow 00:38:28.790$ when they self administer heroin,

NOTE Confidence: 0.9006337666666667

00:38:28.790 --> 00:38:30.875 just like humans,

NOTE Confidence: 0.9006337666666667

 $00:38:30.875 \rightarrow 00:38:34.350$ the environmental context becomes important.

NOTE Confidence: 0.9006337666666667

00:38:34.350 --> 00:38:35.862 And for example if you showed

NOTE Confidence: 0.9006337666666667

00:38:35.862 --> 00:38:36.870 them a cue or

NOTE Confidence: 0.848867088

 $00:38:36.931 \longrightarrow 00:38:39.043$ an odor when they get the drug then

NOTE Confidence: 0.848867088

 $00:38:39.043 \rightarrow 00:38:41.390$ they will start to associate those cues.

NOTE Confidence: 0.848867088

 $00{:}38{:}41{.}390 \dashrightarrow 00{:}38{:}42{.}692$ And if you only show them those

NOTE Confidence: 0.848867088

 $00:38:42.692 \rightarrow 00:38:43.948$ cues they will press the lever.

NOTE Confidence: 0.848867088

 $00:38:43.950 \longrightarrow 00:38:45.786$ A lot of that's what we we call it.

NOTE Confidence: 0.848867088

 $00{:}38{:}45{.}790 \dashrightarrow 00{:}38{:}48{.}175$ Seeking behavior and CBD was

NOTE Confidence: 0.848867088

 $00:38:48.175 \longrightarrow 00:38:51.620$ 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

 $00:38:54.040 \dashrightarrow 00:38:57.596$ 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
- $00:38:59.424 \rightarrow 00:39:01.108$ the brains of human hearing users,
- NOTE Confidence: 0.848867088
- $00{:}39{:}01{.}110 \dashrightarrow 00{:}39{:}03{.}366$ 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
- $00:39:05.120 \longrightarrow 00:39:07.520$ We also see those in animals
- NOTE Confidence: 0.848867088
- $00{:}39{:}07{.}520 \dashrightarrow 00{:}39{:}09{.}473$ that self administer heroin and
- NOTE Confidence: 0.848867088
- $00{:}39{:}09{.}473 \dashrightarrow 00{:}39{:}11{.}944$ when we gave those animals CBD to
- NOTE Confidence: 0.848867088
- $00:39:11.944 \rightarrow 00:39:13.639$ actually reverse those changes,
- NOTE Confidence: 0.848867088
- $00:39:13.640 \longrightarrow 00:39:14.920$ we could also see changes,
- NOTE Confidence: 0.848867088
- $00:39:14.920 \rightarrow 00:39:16.660$ for example with with heroin supply,
- NOTE Confidence: 0.848867088
- $00:39:16.660 \rightarrow 00:39:18.840$ administration of the cannabinoid receptor,
- NOTE Confidence: 0.848867088
- $00:39{:}18.840 \dashrightarrow 00{:}39{:}20.740$ and the cannabinoid receptor is
- NOTE Confidence: 0.848867088
- $00{:}39{:}20.740 \dashrightarrow 00{:}39{:}22.260$ very critical for regulating.
- NOTE Confidence: 0.848867088
- $00:39:22.260 \longrightarrow 00:39:24.860$ About the transmission and
- NOTE Confidence: 0.848867088
- $00:39:24.860 \dashrightarrow 00:39:27.460$ CBD normalized those changes.
- NOTE Confidence: 0.848867088
- $00:39:27.460 \longrightarrow 00:39:29.504$ So the question was,
- NOTE Confidence: 0.848867088

 $00:39:29.504 \rightarrow 00:39:32.373$ could it be effective in clinically?

NOTE Confidence: 0.848867088

00:39:32.373 --> 00:39:34.877 And so we ran a number of pilots

NOTE Confidence: 0.848867088

00:39:34.877 --> 00:39:36.019 here as a double.

NOTE Confidence: 0.848867088

 $00:39:36.020 \rightarrow 00:39:37.856$ All of them were double blinded

NOTE Confidence: 0.848867088

00:39:37.856 --> 00:39:39.080 and randomized placebo controls,

NOTE Confidence: 0.848867088

00:39:39.080 --> 00:39:40.774 and those are things I think that

NOTE Confidence: 0.848867088

 $00:39:40.774 \longrightarrow 00:39:42.268$ are really critical when you're

NOTE Confidence: 0.848867088

00:39:42.268 --> 00:39:43.339 talking about cannabinoids,

NOTE Confidence: 0.848867088

 $00{:}39{:}43{.}340 \dashrightarrow 00{:}39{:}45{.}195$ and especially today where every body

NOTE Confidence: 0.848867088

 $00{:}39{:}45.195 \dashrightarrow 00{:}39{:}47.050$ thinks that cannabis in general

NOTE Confidence: 0.848867088

00:39:47.111 --> 00:39:49.139 may be treatment for everything but

NOTE Confidence: 0.848867088

 $00{:}39{:}49{.}139 \dashrightarrow 00{:}39{:}50{.}955$ those cannabis studies are difficult

NOTE Confidence: 0.848867088

00:39:50.955 --> 00:39:52.955 because especially if they're THC,

NOTE Confidence: 0.848867088

 $00:39:52.960 \rightarrow 00:39:55.120$ people know when they're getting THC

NOTE Confidence: 0.848867088

 $00:39:55.120 \rightarrow 00:39:57.208$ with CBD, it doesn't have intoxicating.

NOTE Confidence: 0.848867088

 $00:39:57.208 \rightarrow 00:40:00.128$ Properties so at least we can have you know,

00:40:00.130 --> 00:40:01.942 good placebo control studies.

NOTE Confidence: 0.848867088

 $00{:}40{:}01{.}942 \dashrightarrow 00{:}40{:}05{.}134$ 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

 $00{:}40{:}07{.}899 \dashrightarrow 00{:}40{:}10{.}311$ 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

 $00{:}40{:}12.640 \dashrightarrow 00{:}40{:}15.316$ they crave and CBD reduced that.

NOTE Confidence: 0.848867088

 $00:40:15.320 \longrightarrow 00:40:17.315$ So replicating what we saw in the

NOTE Confidence: 0.848867088

 $00{:}40{:}17.315 \dashrightarrow 00{:}40{:}19.598$ animals in the in terms of their

NOTE Confidence: 0.848867088

 $00{:}40{:}19.598 \dashrightarrow 00{:}40{:}20.618$ drug seeking behavior.

NOTE Confidence: 0.848867088

 $00{:}40{:}20.620 \dashrightarrow 00{:}40{:}22.528$ One of the things that animals

NOTE Confidence: 0.848867088

 $00:40:22.528 \rightarrow 00:40:24.897$ study had also showed us was that

NOTE Confidence: 0.848867088

 $00{:}40{:}24.897 \dashrightarrow 00{:}40{:}26.955$ even weeks after the last CBD

NOTE Confidence: 0.848867088

 $00:40:26.955 \longrightarrow 00:40:28.279$ administration to the animals,

NOTE Confidence: 0.848867088

 $00:40:28.280 \longrightarrow 00:40:29.915$ it was still reducing their

NOTE Confidence: 0.848867088

 $00{:}40{:}29{.}915 \dashrightarrow 00{:}40{:}30{.}896$ hero in seeking behavior.

 $00:40:30.900 \longrightarrow 00:40:32.556$ So when we brought people back

NOTE Confidence: 0.848867088

 $00{:}40{:}32.556 \dashrightarrow 00{:}40{:}34.606$ into the lab about a week later,

NOTE Confidence: 0.848867088

 $00:40:34.606 \longrightarrow 00:40:37.497$ 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

 $00:40:39.610 \longrightarrow 00:40:41.116$ One thing that we also saw,

NOTE Confidence: 0.848867088

 $00:40:41.120 \longrightarrow 00:40:43.983$ at least the our study participant would

NOTE Confidence: 0.848867088

 $00{:}40{:}43{.}983 \dashrightarrow 00{:}40{:}47{.}569$ clear was CBD was also impacting on anxiety,

NOTE Confidence: 0.848867088

 $00:40:47.570 \rightarrow 00:40:49.649$ so when they had gotten the heroin,

NOTE Confidence: 0.848867088

 $00{:}40{:}49{.}650 \dashrightarrow 00{:}40{:}52{.}146$ Hugh and and been given placebo,

NOTE Confidence: 0.848867088

 $00:40:52.150 \longrightarrow 00:40:53.974$ they they were anxious and when

NOTE Confidence: 0.848867088

 $00:40:53.974 \longrightarrow 00:40:56.368$ they got to CBD it reduced the

NOTE Confidence: 0.848867088

 $00{:}40{:}56{.}368 \dashrightarrow 00{:}40{:}58{.}223$ anxiety that cue induced again.

NOTE Confidence: 0.848867088

 $00{:}40{:}58.230 \dashrightarrow 00{:}41{:}01.219$ Cue induced angularity and a week later

NOTE Confidence: 0.848867088

 $00:41:01.219 \longrightarrow 00:41:03.610$ it's still reduced their anxiety.

NOTE Confidence: 0.848867088

 $00:41:03.610 \longrightarrow 00:41:05.020$ We hadn't studied anxiety in

NOTE Confidence: 0.848867088

 $00:41:05.020 \rightarrow 00:41:05.866$ our animal models,

- NOTE Confidence: 0.848867088
- $00:41:05.870 \longrightarrow 00:41:07.678$ but we did try to look at other
- NOTE Confidence: 0.848867088
- 00:41:07.678 --> 00:41:10.470 aspects of in terms of, you know,
- NOTE Confidence: 0.848867088
- $00:41:10.470 \longrightarrow 00:41:13.046$ in our human studies in not just the
- NOTE Confidence: 0.848867088
- 00:41:13.046 --> 00:41:15.270 self reports of craving and anxiety,
- NOTE Confidence: 0.848867088
- $00:41:15.270 \longrightarrow 00:41:16.550$ but also these physiological
- NOTE Confidence: 0.848867088
- $00{:}41{:}16.550 \dashrightarrow 00{:}41{:}17.510$ measures of stress.
- NOTE Confidence: 0.848867088
- $00:41:17.510 \longrightarrow 00:41:19.334$ For example, cortisol levels.
- NOTE Confidence: 0.848867088
- $00{:}41{:}19{.}334 \dashrightarrow 00{:}41{:}22{.}505$ So when when people had been given
- NOTE Confidence: 0.848867088
- $00{:}41{:}22.505 \dashrightarrow 00{:}41{:}25.550$ the drug queue and had gotten placebo,
- NOTE Confidence: 0.848867088
- $00:41:25.550 \longrightarrow 00:41:27.550$ their cortisol levels went up
- NOTE Confidence: 0.848867088
- $00{:}41{:}27{.}550 \dashrightarrow 00{:}41{:}29{.}150$ and CBD reduced that.
- NOTE Confidence: 0.848867088
- 00:41:29.150 --> 00:41:29.566 Similarly,
- NOTE Confidence: 0.848867088
- $00:41:29.566 \rightarrow 00:41:32.894$ their heart rate went up when given the
- NOTE Confidence: 0.848867088
- $00{:}41{:}32.894 \dashrightarrow 00{:}41{:}36.256$ drug queue and placebo and CBE reduce that.
- NOTE Confidence: 0.848867088
- 00:41:36.260 --> 00:41:37.148 As I said,
- NOTE Confidence: 0.848867088

 $00:41:37.148 \rightarrow 00:41:39.220$ we hadn't really looked at anxiety in

NOTE Confidence: 0.789302832307692

 $00:41:39.288 \longrightarrow 00:41:41.316$ our animal models, but based on what

NOTE Confidence: 0.789302832307692

 $00:41:41.316 \rightarrow 00:41:43.420$ we we were we saw in our humans,

NOTE Confidence: 0.789302832307692

 $00:41:43.420 \rightarrow 00:41:45.620$ we've now gone back to look at that

NOTE Confidence: 0.789302832307692

 $00{:}41{:}45.620 \dashrightarrow 00{:}41{:}48.080$ and to also try to understand what's

NOTE Confidence: 0.789302832307692

 $00:41:48.080 \longrightarrow 00:41:50.291$ 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

 $00:41:52.972 \rightarrow 00:41:55.415$ that Jackie Ferlin we looked at,

NOTE Confidence: 0.789302832307692

 $00:41:55.415 \longrightarrow 00:41:58.169$ we tried to induce anxiety in our

NOTE Confidence: 0.789302832307692

 $00{:}41{:}58.169 \dashrightarrow 00{:}42{:}00.430$ animals plastic with in terms of shocking

NOTE Confidence: 0.789302832307692

 $00{:}42{:}00{.}492 \dashrightarrow 00{:}42{:}02{.}858$ animals and when the animals are shocked,

NOTE Confidence: 0.789302832307692

 $00:42:02.860 \longrightarrow 00:42:03.924$ they're given a queue.

NOTE Confidence: 0.789302832307692

 $00:42:03.924 \rightarrow 00:42:05.859$ Here we give them this lemon odor

NOTE Confidence: 0.789302832307692

 $00:42:05.859 \rightarrow 00:42:07.557$ and then we assess their anxiety.

NOTE Confidence: 0.789302832307692

 $00:42:07.560 \longrightarrow 00:42:08.736$ Related behavior here.

NOTE Confidence: 0.789302832307692

 $00:42:08.736 \longrightarrow 00:42:11.480$ This is using the light dark spots
- NOTE Confidence: 0.789302832307692
- $00:42:11.552 \longrightarrow 00:42:13.862$ and we could see that in those
- NOTE Confidence: 0.789302832307692
- $00:42:13.862 \rightarrow 00:42:16.074$ animals that when they've been given
- NOTE Confidence: 0.789302832307692
- $00{:}42{:}16.074 \dashrightarrow 00{:}42{:}18.350$ vehicle and they had were exposed
- NOTE Confidence: 0.789302832307692
- $00:42:18.350 \longrightarrow 00:42:21.825$ to the lemon queue and they showed
- NOTE Confidence: 0.789302832307692
- $00{:}42{:}21.825 \dashrightarrow 00{:}42{:}24.485$ increased anxiety related behavior.
- NOTE Confidence: 0.789302832307692
- 00:42:24.490 --> 00:42:27.850 But given CBD CBD completely reduced,
- NOTE Confidence: 0.789302832307692
- $00{:}42{:}27.850 \dashrightarrow 00{:}42{:}30.790$ that Q induced limit.
- NOTE Confidence: 0.789302832307692
- $00:42:30.790 \longrightarrow 00:42:31.730$ Behavioral response.
- NOTE Confidence: 0.789302832307692
- 00:42:31.730 --> 00:42:34.080 We're now, as I said,
- NOTE Confidence: 0.789302832307692
- 00:42:34.080 --> 00:42:35.610 trying to understand how CBD
- NOTE Confidence: 0.789302832307692
- $00:42:35.610 \rightarrow 00:42:37.140$ might be having its effects,
- NOTE Confidence: 0.789302832307692
- $00:42:37.140 \longrightarrow 00:42:40.896$ so that we can perhaps identify
- NOTE Confidence: 0.789302832307692
- $00{:}42{:}40.896 \dashrightarrow 00{:}42{:}43.841$ even non CBD related development.
- NOTE Confidence: 0.789302832307692
- $00{:}42{:}43{.}841 \dashrightarrow 00{:}42{:}46{.}487$ Non CBD related medications based on
- NOTE Confidence: 0.789302832307692
- $00{:}42{:}46{.}487 \dashrightarrow 00{:}42{:}49{.}238$ the the biology of what's happening.
- NOTE Confidence: 0.789302832307692

00:42:49.240 --> 00:42:51.336 Not going to tell you some of the

NOTE Confidence: 0.789302832307692

 $00{:}42{:}51{.}340 \dashrightarrow 00{:}42{:}53{.}938$ the specific mechanisms that we see,

NOTE Confidence: 0.789302832307692

 $00{:}42{:}53{.}940 \dashrightarrow 00{:}42{:}56{.}164$ but one of the things that's clear is

NOTE Confidence: 0.789302832307692

 $00:42:56.164 \rightarrow 00:42:58.239$ that there are disturbances in these

NOTE Confidence: 0.789302832307692

 $00{:}42{:}58{.}240 \dashrightarrow 00{:}43{:}00{.}298$ circuits related to the nucleus accumbens.

NOTE Confidence: 0.789302832307692

 $00:43:00.300 \rightarrow 00:43:02.930$ The basolateral amygdala and prelimbic.

NOTE Confidence: 0.789302832307692

00:43:02.930 --> 00:43:04.574 Facts, not surprisingly,

NOTE Confidence: 0.789302832307692

00:43:04.574 --> 00:43:05.670 but interestingly,

NOTE Confidence: 0.789302832307692

 $00{:}43{:}05{.}670 \dashrightarrow 00{:}43{:}06{.}680$ if we just, for example,

NOTE Confidence: 0.789302832307692

 $00:43:06.680 \rightarrow 00:43:07.672$ within the nucleus accumbens,

NOTE Confidence: 0.789302832307692

 $00:43:07.672 \longrightarrow 00:43:08.912$ here is just a shell.

NOTE Confidence: 0.789302832307692

 $00:43:08.920 \longrightarrow 00:43:10.621$ We can see that there is a

NOTE Confidence: 0.789302832307692

 $00:43:10.621 \rightarrow 00:43:11.989$ significant changes where some genes

NOTE Confidence: 0.789302832307692

 $00:43:11.989 \rightarrow 00:43:13.459$ are downregulated in other genes,

NOTE Confidence: 0.789302832307692

 $00:43:13.460 \rightarrow 00:43:15.790$ upregulated when in animals when

NOTE Confidence: 0.789302832307692

 $00:43:15.790 \longrightarrow 00:43:18.120$ they're exposed again to this,

- NOTE Confidence: 0.789302832307692
- $00:43:18.120 \longrightarrow 00:43:20.160$ this queuing juice stressor and
- NOTE Confidence: 0.789302832307692
- 00:43:20.160 00:43:22.200 they show this anxiety behavior,
- NOTE Confidence: 0.789302832307692
- $00{:}43{:}22{.}200 \dashrightarrow 00{:}43{:}24{.}279$ and when you look at the animals
- NOTE Confidence: 0.789302832307692
- $00:43:24.279 \longrightarrow 00:43:26.478$ that had gotten CBD and their
- NOTE Confidence: 0.789302832307692
- $00:43:26.478 \longrightarrow 00:43:27.717$ behaviors were normalized.
- NOTE Confidence: 0.789302832307692
- 00:43:27.720 --> 00:43:30.198 It's just it shows that CBD
- NOTE Confidence: 0.789302832307692
- $00{:}43{:}30{.}198 \dashrightarrow 00{:}43{:}32{.}426$ reverses or even eliminates these
- NOTE Confidence: 0.789302832307692
- $00:43:32.426 \rightarrow 00:43:34.926$ particular genes that are changed.
- NOTE Confidence: 0.789302832307692
- 00:43:34.930 --> 00:43:37.920 So. Does cannabidiol hold promise?
- NOTE Confidence: 0.789302832307692
- $00:43:37.920 \longrightarrow 00:43:39.051$ At least here,
- NOTE Confidence: 0.789302832307692
- $00:43:39.051 \rightarrow 00:43:41.325$ we've been able to do clinical trials.
- NOTE Confidence: 0.789302832307692
- 00:43:41.325 --> 00:43:42.855 We're still working on one of
- NOTE Confidence: 0.789302832307692
- $00:43:42.855 \longrightarrow 00:43:43.939$ the effective doses,
- NOTE Confidence: 0.789302832307692
- $00{:}43{:}43{.}940 \dashrightarrow 00{:}43{:}45{.}460$ and the formulations and
- NOTE Confidence: 0.789302832307692
- $00:43:45.460 \longrightarrow 00:43:46.600$ the delivery systems,
- NOTE Confidence: 0.789302832307692

00:43:46.600 --> 00:43:50.219 but similar to what we you know

NOTE Confidence: 0.789302832307692

00:43:50.220 --> 00:43:52.922 I mentioned in terms of the other

NOTE Confidence: 0.789302832307692

 $00{:}43{:}52{.}922 \dashrightarrow 00{:}43{:}55{.}529$ strategies that we're looking at in

NOTE Confidence: 0.789302832307692

 $00:43:55.529 \rightarrow 00:43:57.343$ translating to developing potential

NOTE Confidence: 0.789302832307692

 $00:43:57.343 \longrightarrow 00:43:59.558$ medications for opiate use disorder.

NOTE Confidence: 0.789302832307692

 $00:43:59.560 \rightarrow 00:44:03.052$ It may not be specific CBD for just opioids.

NOTE Confidence: 0.789302832307692

 $00:44:03.060 \rightarrow 00:44:04.284$ Other groups have shown,

NOTE Confidence: 0.789302832307692

 $00:44:04.284 \rightarrow 00:44:06.256$ for example, with alcohol again.

NOTE Confidence: 0.789302832307692

 $00{:}44{:}06{.}256 \dashrightarrow 00{:}44{:}08{.}516$ And here weeks after their

NOTE Confidence: 0.789302832307692

 $00:44:08.516 \longrightarrow 00:44:10.650$ last alcohol intake animals,

NOTE Confidence: 0.789302832307692

 $00{:}44{:}10.650 \dashrightarrow 00{:}44{:}13.060$ CBD still reduce their alcohol

NOTE Confidence: 0.789302832307692

 $00:44:13.060 \rightarrow 00:44:14.024$ seeking behavior.

NOTE Confidence: 0.789302832307692

 $00:44:14.030 \rightarrow 00:44:16.641$ And even when they're the stress induced

NOTE Confidence: 0.789302832307692

 $00:44:16.641 \rightarrow 00:44:18.718$ against here, it's just a shock.

NOTE Confidence: 0.789302832307692

 $00{:}44{:}18.718 \dashrightarrow 00{:}44{:}19.050$ Again.

NOTE Confidence: 0.789302832307692

00:44:19.050 --> 00:44:21.521 You can also see that CBD still

- NOTE Confidence: 0.789302832307692
- $00:44:21.521 \rightarrow 00:44:23.810$ reduce their alcohol seeking behavior.
- NOTE Confidence: 0.789302832307692
- $00:44:23.810 \longrightarrow 00:44:27.456$ But there may be some things that would sex.
- NOTE Confidence: 0.789302832307692
- $00:44:27.456 \longrightarrow 00:44:28.362$ For example,
- NOTE Confidence: 0.789302832307692
- $00:44:28.362 \longrightarrow 00:44:31.080$ a group looking at binge drinking
- NOTE Confidence: 0.789302832307692
- $00:44:31.159 \longrightarrow 00:44:33.882$ 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
- $00{:}44{:}38{.}378 \dashrightarrow 00{:}44{:}41{.}420$ it did not do that in the female until
- NOTE Confidence: 0.789302832307692
- $00{:}44{:}41{.}492 \dashrightarrow 00{:}44{:}44{.}045$ they increased the dose of CBD significantly.
- NOTE Confidence: 0.789302832307692
- $00:44:44.045 \longrightarrow 00:44:47.205$ 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
- $00{:}44{:}49.682 \dashrightarrow 00{:}44{:}52.627$ but at least now we're able to
- NOTE Confidence: 0.789302832307692
- $00{:}44{:}52.627 \dashrightarrow 00{:}44{:}54.717$ expand our our small studies.
- NOTE Confidence: 0.767624137117647
- $00{:}44{:}54{.}720 \dashrightarrow 00{:}44{:}57{.}750$ And now we're also looking at in terms of a
- NOTE Confidence: 0.767624137117647
- $00:44:57.820 \rightarrow 00:45:00.774$ 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 place bo control,

NOTE Confidence: 0.767624137117647

 $00:45:04.179 \rightarrow 00:45:06.790$ and to see also doing your imaging

NOTE Confidence: 0.767624137117647

 $00{:}45{:}06.855 \dashrightarrow 00{:}45{:}09.023$ studies to see if we can start in

NOTE Confidence: 0.767624137117647

 $00{:}45{:}09{.}023 \dashrightarrow 00{:}45{:}11{.}046$ humans like our animal models to

NOTE Confidence: 0.767624137117647

 $00{:}45{:}11.046 \dashrightarrow 00{:}45{:}12.821$ understand what are the neural

NOTE Confidence: 0.767624137117647

 $00:45:12.821 \rightarrow 00:45:15.750$ systems that are changed with CBD.

NOTE Confidence: 0.767624137117647

 $00:45:15.750 \rightarrow 00:45:21.110$ So clearly in looking at the human brain,

NOTE Confidence: 0.767624137117647

 $00:45:21.110 \longrightarrow 00:45:23.648$ it has taught us a lot that you know,

NOTE Confidence: 0.767624137117647

 $00:45:23.650 \rightarrow 00:45:25.680$ although initially we have focused

NOTE Confidence: 0.767624137117647

 $00{:}45{:}25.680 \dashrightarrow 00{:}45{:}28.566$ on dopamine and and even the opioid

NOTE Confidence: 0.767624137117647

 $00:45:28.566 \rightarrow 00:45:30.792$ system in targeting for medication,

NOTE Confidence: 0.767624137117647

 $00{:}45{:}30.792 \dashrightarrow 00{:}45{:}34.102$ but it's about epigenetics and

NOTE Confidence: 0.767624137117647

 $00:45:34.102 \longrightarrow 00:45:37.359$ synaptic plasticity and these to

NOTE Confidence: 0.767624137117647

 $00{:}45{:}37{.}359 \dashrightarrow 00{:}45{:}41{.}217$ me and also those those neural.

NOTE Confidence: 0.767624137117647

 $00:45:41.220 \rightarrow 00:45:44.016$ Networks and those systems that really

NOTE Confidence: 0.767624137117647

 $00:45:44.016 \rightarrow 00:45:46.867$ 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

 $00:45:50.200 \longrightarrow 00:45:52.220$ and the important thing about

NOTE Confidence: 0.767624137117647

 $00{:}45{:}52{.}220 \dashrightarrow 00{:}45{:}54{.}240$ all of these epigenetic changes

NOTE Confidence: 0.767624137117647

 $00:45:54.313 \longrightarrow 00:45:56.168$ is that they are reversible.

NOTE Confidence: 0.767624137117647

00:45:56.170 --> 00:45:57.078 So yes,

NOTE Confidence: 0.767624137117647

 $00:45:57.078 \rightarrow 00:45:59.348$ the epigenetic mechanisms maintain these

NOTE Confidence: 0.767624137117647

 $00{:}45{:}59{.}348 \dashrightarrow 00{:}46{:}01{.}620$ long term sensitivity of the brain,

NOTE Confidence: 0.767624137117647

 $00:46:01.620 \rightarrow 00:46:03.314$ but it's because we really haven't found

NOTE Confidence: 0.767624137117647

 $00:46:03.314 \rightarrow 00:46:04.759$ the right targets to reverse them,

NOTE Confidence: 0.767624137117647

 $00:46:04.760 \longrightarrow 00:46:07.418$ because these tags are like genetics,

NOTE Confidence: 0.767624137117647

 $00{:}46{:}07{.}420 \dashrightarrow 00{:}46{:}08{.}056$ are reversible.

NOTE Confidence: 0.767624137117647

 $00{:}46{:}08.056 \dashrightarrow 00{:}46{:}11.150$ So I had mentioned a lot of the people.

NOTE Confidence: 0.767624137117647

 $00:46:11.150 \longrightarrow 00:46:12.370$ Who had you know,

NOTE Confidence: 0.767624137117647

 $00:46:12.370 \longrightarrow 00:46:14.200$ contributed to a lot of the

NOTE Confidence: 0.767624137117647

 $00:46:14.275 \longrightarrow 00:46:15.767$ 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

 $00{:}46{:}20.710 \dashrightarrow 00{:}46{:}22.462$ and a lot of our clinical

NOTE Confidence: 0.767624137117647

 $00{:}46{:}22.462 \dashrightarrow 00{:}46{:}23.630$ team and Karen backing,

NOTE Confidence: 0.767624137117647

 $00{:}46{:}23.630 \dashrightarrow 00{:}46{:}26.157$ and in large part in running the

NOTE Confidence: 0.767624137117647

 $00{:}46{:}26.157 \dashrightarrow 00{:}46{:}28.363$ operations of our clinical trials

NOTE Confidence: 0.767624137117647

 $00{:}46{:}28.363 \dashrightarrow 00{:}46{:}31.201$ and doctor and soul systems of

NOTE Confidence: 0.767624137117647

 $00{:}46{:}31{.}201 \dashrightarrow 00{:}46{:}33{.}370$ Amazing Addiction medicine physician

NOTE Confidence: 0.767624137117647

 $00:46:33.370 \longrightarrow 00:46:35.026$ who's been great to work with.

NOTE Confidence: 0.767624137117647

 $00:46:35.030 \longrightarrow 00:46:36.955$ So with that I will take any

NOTE Confidence: 0.767624137117647

 $00:46:36.955 \rightarrow 00:46:38.489$ questions that you might have.

NOTE Confidence: 0.767624137117647

00:46:38.490 --> 00:46:40.000 Thank you.