WEBVTT

NOTE duration:"00:11:05.8240000"

NOTE language:en-us

NOTE Confidence: 0.832422

00:00:00.000 --> 00:00:03.157 Hi everyone, welcome to the Yale Psychiatry

NOTE Confidence: 0.832422

00:00:03.157 --> 00:00:05.890 and Child Study center datablitz.

NOTE Confidence: 0.832422

00:00:05.890 --> 00:00:08.274 I'm happy to share with you some of

NOTE Confidence: 0.832422

00:00:08.274 --> 00:00:10.719 my work on Astral cooling signaling

NOTE Confidence: 0.832422

00:00:10.719 --> 00:00:13.383 and how it affects behaviors related

NOTE Confidence: 0.832422

00:00:13.453 --> 00:00:16.071 to stress in mice and how that's

NOTE Confidence: 0.832422

00:00:16.071 --> 00:00:18.690 translatable to human subjects.

NOTE Confidence: 0.832422

00:00:18.690 --> 00:00:20.741 I'm going to share my screen now

NOTE Confidence: 0.832422

00:00:20.741 --> 00:00:22.813 and show you some of the work

NOTE Confidence: 0.832422

00:00:22.813 --> 00:00:24.493 that's going on in my lab.

NOTE Confidence: 0.832422

00:00:24.500 --> 00:00:26.365 Our laboratory is interested in

NOTE Confidence: 0.832422

00:00:26.365 --> 00:00:28.678 the receptors for nicotine in the

NOTE Confidence: 0.832422

00:00:28.678 --> 00:00:30.952 brain and how those affect behaviors

NOTE Confidence: 0.832422

00:00:30.952 --> 00:00:32.975 in typical situations and also

NOTE Confidence: 0.832422

00:00:32.975 --> 00:00:34.607 related to psychiatric illness.

NOTE Confidence: 0.832422

00:00:34.610 --> 00:00:37.123 One thing we know is that smoking

NOTE Confidence: 0.832422

00:00:37.123 --> 00:00:39.127 anxiety and depression are highly

NOTE Confidence: 0.832422

00:00:39.127 --> 00:00:40.839 correlated in human subjects.

NOTE Confidence: 0.832422

00:00:40.840 --> 00:00:42.780 We know that major depressive

NOTE Confidence: 0.832422

00:00:42.780 --> 00:00:44.736 disorder is a chronic, debilitating,

NOTE Confidence: 0.832422

00:00:44.736 --> 00:00:45.528 relapsing illness.

NOTE Confidence: 0.832422

00:00:45.528 --> 00:00:47.904 The huge cost to the individual

NOTE Confidence: 0.832422

00:00:47.904 --> 00:00:49.788 to families and to society,

NOTE Confidence: 0.832422

00:00:49.790 --> 00:00:51.342 and there's a bidirectional

NOTE Confidence: 0.832422

00:00:51.342 --> 00:00:52.506 relationship with smoking.

NOTE Confidence: 0.832422

00:00:52.510 --> 00:00:54.685 People who are depressed or

NOTE Confidence: 0.832422

00:00:54.685 --> 00:00:56.425 more likely to smoke.

NOTE Confidence: 0.832422

00:00:56.430 --> 00:00:58.015 And people who smoke are

NOTE Confidence: 0.832422

00:00:58.015 --> 00:00:59.600 more likely to be depressed,

NOTE Confidence: 0.832422

00:00:59.600 --> 00:01:02.165 so about 40 to 60% of patients with

NOTE Confidence: 0.832422

00:01:02.165 --> 00:01:04.115 depression smoke versus now much less

NOTE Confidence: 0.832422

00:01:04.115 --> 00:01:06.586 than 20% of the general population.

NOTE Confidence: 0.832422

00:01:06.586 --> 00:01:09.460 So can we identify the neurobiological

NOTE Confidence: 0.832422

00:01:09.541 --> 00:01:12.417 mechanisms underlying this comorbidity?

NOTE Confidence: 0.832422

00:01:12.420 --> 00:01:14.737 Where should tell you that the primary

NOTE Confidence: 0.832422

00:01:14.737 --> 00:01:17.310 targets for nicotine in the brain or

NOTE Confidence: 0.832422

00:01:17.310 --> 00:01:18.826 the nicotinic acetylcholine receptors?

NOTE Confidence: 0.832422

00:01:18.830 --> 00:01:20.456 These are a family of receptors

NOTE Confidence: 0.832422

00:01:20.456 --> 00:01:21.976 that respond to the endogenous

NOTE Confidence: 0.832422

00:01:21.976 --> 00:01:23.504 neurotransmitter acetal choline and

NOTE Confidence: 0.832422

00:01:23.504 --> 00:01:26.343 there are two families of Astle calling

NOTE Confidence: 0.832422

00:01:26.343 --> 00:01:28.079 receptors nicotinic and muscarinic.

NOTE Confidence: 0.832422

00:01:28.080 --> 00:01:30.568 And I'm going to tell you about the

NOTE Confidence: 0.832422

00:01:30.568 --> 00:01:32.075 relationship between the nicotinic

NOTE Confidence: 0.832422

00:01:32.075 --> 00:01:34.140 receptors and Astle calling signaling.

NOTE Confidence: 0.832422

00:01:34.140 --> 00:01:36.198 Today we have projects and muscarinic

NOTE Confidence: 0.832422

00:01:36.198 --> 00:01:38.363 receptors as well as still calling

NOTE Confidence: 0.832422

00:01:38.363 --> 00:01:40.897 neurons in the brain project very widely.

NOTE Confidence: 0.832422

00:01:40.900 --> 00:01:43.168 Their cell bodies in the basil.

NOTE Confidence: 0.832422

00:01:43.170 --> 00:01:45.676 Or bring complex and in the brainstem

NOTE Confidence: 0.832422

00:01:45.676 --> 00:01:48.317 project pretty much everywhere in the brain,

NOTE Confidence: 0.832422

00:01:48.320 --> 00:01:51.264 and in addition number of studies have shown,

NOTE Confidence: 0.832422

00:01:51.270 --> 00:01:53.466 and here's one from the 1990s.

NOTE Confidence: 0.832422

00:01:53.470 --> 00:01:55.642 That stress induces us to cooling

NOTE Confidence: 0.832422

00:01:55.642 --> 00:01:57.889 release in many different brain areas.

NOTE Confidence: 0.832422

00:01:57.890 --> 00:02:00.459 And so you can see here that

NOTE Confidence: 0.832422

00:02:00.459 --> 00:02:01.586 using microdialysis, restraint,

NOTE Confidence: 0.832422

00:02:01.586 --> 00:02:03.902 stress results in elevations of Astle

NOTE Confidence: 0.832422

00:02:03.902 --> 00:02:05.620 calling signaling throughout the brain,

NOTE Confidence: 0.832422

00:02:05.620 --> 00:02:08.632 including the hippocampus for as long

NOTE Confidence: 0.832422

00:02:08.632 --> 00:02:11.620 as that restraint stress is applied.

NOTE Confidence: 0.832422

00:02:11.620 --> 00:02:14.180 So what we've done is to use biochemical

NOTE Confidence: 0.832422

00:02:14.180 --> 00:02:15.898 and molecular biological techniques

NOTE Confidence: 0.832422

00:02:15.898 --> 00:02:18.438 to manipulate Astle calling signaling,

NOTE Confidence: 0.832422

00:02:18.440 --> 00:02:20.840 and in this experiment from 2013,

NOTE Confidence: 0.832422

00:02:20.840 --> 00:02:23.486 what we did was to block Astle

NOTE Confidence: 0.832422

00:02:23.486 --> 00:02:25.107 calling breakdown throughout the

NOTE Confidence: 0.832422

00:02:25.107 --> 00:02:27.609 brain and body by using the

NOTE Confidence: 0.832422

00:02:27.609 --> 00:02:28.860 pharmacological antagonist Astle.

NOTE Confidence: 0.832422

00:02:28.860 --> 00:02:30.468 Colon especial cholinesterase antagonist,

NOTE Confidence: 0.832422

00:02:30.468 --> 00:02:30.870 physostigmine,

NOTE Confidence: 0.832422

00:02:30.870 --> 00:02:34.166 and what we saw was that there was

NOTE Confidence: 0.832422

00:02:34.166 --> 00:02:36.478 more immobility in this one test.

NOTE Confidence: 0.832422

00:02:36.480 --> 00:02:37.797 We used many,

NOTE Confidence: 0.832422

00:02:37.797 --> 00:02:40.431 but I'm showing you the tail

NOTE Confidence: 0.832422

00:02:40.431 --> 00:02:42.527 suspension here as an example.

NOTE Confidence: 0.832422

00:02:42.530 --> 00:02:44.564 You got more reactivity to stress

NOTE Confidence: 0.832422

00:02:44.564 --> 00:02:47.366 as we increase the dose of this

NOTE Confidence: 0.832422

00:02:47.366 --> 00:02:48.737 Astle cholinesterase blocker,

NOTE Confidence: 0.832422

00:02:48.740 --> 00:02:50.675 which means as overall levels

NOTE Confidence: 0.832422

00:02:50.675 --> 00:02:52.223 of actual calling increased,

NOTE Confidence: 0.832422

00:02:52.230 --> 00:02:54.558 we got more stress related behaviors.

NOTE Confidence: 0.832422

00:02:54.560 --> 00:02:56.882 These could be reversed by blockers

NOTE Confidence: 0.832422

00:02:56.882 --> 00:02:58.444 of either nicotinic, muscarinic,

NOTE Confidence: 0.832422

00:02:58.444 --> 00:03:00.808 or both families of astral choline

NOTE Confidence: 0.832422

00:03:00.808 --> 00:03:02.789 receptors and that makes sense

NOTE Confidence: 0.832422

00:03:02.789 --> 00:03:05.003 because that means that this increase

NOTE Confidence: 0.832422

00:03:05.003 --> 00:03:06.974 in national calling resulted in

NOTE Confidence: 0.832422

00:03:06.974 --> 00:03:08.526 behaviors that were sensitive

NOTE Confidence: 0.832422

00:03:08.526 --> 00:03:10.494 to colon estel choline receptor

NOTE Confidence: 0.832422

00:03:10.494 --> 00:03:12.906 blockers and you can see that.

NOTE Confidence: 0.832422

00:03:12.910 --> 00:03:14.143 The behavior actually

NOTE Confidence: 0.832422

00:03:14.143 --> 00:03:15.787 went down below baseline,

NOTE Confidence: 0.8114404

00:03:15.790 --> 00:03:17.020 with these blockers,

NOTE Confidence: 0.8114404

00:03:17.020 --> 00:03:18.660 suggesting that there's hostile

NOTE Confidence: 0.8114404

00:03:18.660 --> 00:03:21.161 calling tone that that is responsible

NOTE Confidence: 0.8114404

00:03:21.161 --> 00:03:22.769 for the baseline immobility.

NOTE Confidence: 0.8114404

00:03:22.770 --> 00:03:25.510 In this in this test.

NOTE Confidence: 0.8114404

00:03:25.510 --> 00:03:27.814 And this was also reversible by

NOTE Confidence: 0.8114404

00:03:27.814 --> 00:03:29.890 giving the SSRI fluoxetine Prozac.

NOTE Confidence: 0.8114404

00:03:29.890 --> 00:03:32.026 So first here's the increase in

NOTE Confidence: 0.8114404

00:03:32.026 --> 00:03:34.604 immobility that we see when we increase

NOTE Confidence: 0.8114404

00:03:34.604 --> 00:03:37.138 Estel coin signaling and that can also

NOTE Confidence: 0.8114404

00:03:37.212 --> 00:03:39.517 be reversed by this antidepressant

NOTE Confidence: 0.8114404

00:03:39.517 --> 00:03:41.822 that's widely prescribed in humans,

NOTE Confidence: 0.8114404

00:03:41.830 --> 00:03:43.876 suggesting that the model that we're

NOTE Confidence: 0.8114404

00:03:43.876 --> 00:03:46.111 looking at is more broadly relevant

NOTE Confidence: 0.8114404

00:03:46.111 --> 00:03:47.723 to depression related behaviors

NOTE Confidence: 0.8114404

00:03:47.723 --> 00:03:50.579 than just to the cholinergic system.

NOTE Confidence: 0.8114404

00:03:50.580 --> 00:03:53.112 And this is related to experiments

NOTE Confidence: 0.8114404

00:03:53.112 --> 00:03:55.879 done back in the 70s and 80s.

NOTE Confidence: 0.8114404

00:03:55.880 --> 00:03:57.704 By David Chrzanowski and his colleagues

NOTE Confidence: 0.8114404

00:03:57.704 --> 00:03:59.687 who gave the same drug Pfizer

NOTE Confidence: 0.8114404

00:03:59.687 --> 00:04:01.829 stigma to humans and saw depressive

NOTE Confidence: 0.8114404

00:04:01.829 --> 00:04:03.560 symptomatology even in human subjects,

NOTE Confidence: 0.8114404

00:04:03.560 --> 00:04:05.898 had never had a history of depression,

NOTE Confidence: 0.8114404

00:04:05.900 --> 00:04:07.595 suggesting that what we're looking

NOTE Confidence: 0.8114404

00:04:07.595 --> 00:04:09.909 at in mice is translatable to humans.

NOTE Confidence: 0.8114404

00:04:09.910 --> 00:04:11.782 Where in the brain is this

NOTE Confidence: 0.8114404

00:04:11.782 --> 00:04:13.805 happening where we were able to

NOTE Confidence: 0.8114404

00:04:13.805 --> 00:04:15.585 use molecular genetics to block,

NOTE Confidence: 0.8114404

00:04:15.590 --> 00:04:16.592 to downregulate Astle?

NOTE Confidence: 0.8114404

00:04:16.592 --> 00:04:17.928 Cholinesterase activity only locally

NOTE Confidence: 0.8114404

00:04:17.928 --> 00:04:18.930 in the hippocampus?

NOTE Confidence: 0.8114404

00:04:18.930 --> 00:04:21.198 I won't walk through all of this

NOTE Confidence: 0.8114404

00:04:21.198 --> 00:04:23.940 for the met up for reasons of time,

NOTE Confidence: 0.8114404

00:04:23.940 --> 00:04:26.612 but what you can see is that when

NOTE Confidence: 0.8114404

00:04:26.612 --> 00:04:27.740 we knocked down.

NOTE Confidence: 0.8114404

00:04:27.740 --> 00:04:29.750 Ask for cholinesterase only in

NOTE Confidence: 0.8114404

00:04:29.750 --> 00:04:30.554 the hippocampus.

NOTE Confidence: 0.8114404

00:04:30.560 --> 00:04:32.646 We see the same phenotype that we

NOTE Confidence: 0.8114404

00:04:32.646 --> 00:04:34.452 see when we pharmacologically block

NOTE Confidence: 0.8114404

00:04:34.452 --> 00:04:36.960 it everywhere and we can rescue

NOTE Confidence: 0.8114404

00:04:36.960 --> 00:04:39.779 that by expressing a human Estel

NOTE Confidence: 0.8114404

00:04:39.779 --> 00:04:41.691 cholinesterase transcript that can't

NOTE Confidence: 0.8114404

00:04:41.691 --> 00:04:44.665 be knocked down in here I'm showing

NOTE Confidence: 0.8114404

00:04:44.665 --> 00:04:46.277 you three different paradigms,

NOTE Confidence: 0.8114404

00:04:46.280 --> 00:04:48.814 both 2 models of immobility but one

NOTE Confidence: 0.8114404

00:04:48.814 --> 00:04:51.110 model of amorphism or ethologically.

NOTE Confidence: 0.8114404

00:04:51.110 --> 00:04:52.020 Relevant stressors.

NOTE Confidence: 0.8114404

00:04:52.020 --> 00:04:54.750 Social defeat stress where we give

NOTE Confidence: 0.8114404

00:04:54.750 --> 00:04:56.778 a subthreshold social defeat and

NOTE Confidence: 0.8114404

00:04:56.778 --> 00:04:59.221 now we see a very potent avoidance.

NOTE Confidence: 0.8114404

00:04:59.230 --> 00:05:02.110 After that social defeat by knocking

NOTE Confidence: 0.8114404

00:05:02.110 --> 00:05:04.030 down Astral cholinesterase only

NOTE Confidence: 0.8114404

00:05:04.107 --> 00:05:05.448 in the hippocampus.

NOTE Confidence: 0.8114404

00:05:05.450 --> 00:05:08.170 So I've shown you some data from our

NOTE Confidence: 0.8114404

00:05:08.170 --> 00:05:09.772 historical experiments showing the

NOTE Confidence: 0.8114404

00:05:09.772 --> 00:05:11.500 increasing Astle calling signaling

NOTE Confidence: 0.8114404

00:05:11.500 --> 00:05:13.674 in hippocampus by decreasing its

NOTE Confidence: 0.8114404

00:05:13.674 --> 00:05:15.218 breakdown increases stress related

NOTE Confidence: 0.8114404

00:05:15.218 --> 00:05:17.540 behaviors in mice to changes in

NOTE Confidence: 0.8114404

00:05:17.540 --> 00:05:19.100 Astral calling signaling than

NOTE Confidence: 0.8114404

00:05:19.100 --> 00:05:21.050 occur and oppressed human subjects.

NOTE Confidence: 0.8114404

00:05:21.050 --> 00:05:23.367 I'm going to show you some data

NOTE Confidence: 0.8114404

00:05:23.367 --> 00:05:25.608 that was gathered by our clinical

NOTE Confidence: 0.8114404

00:05:25.608 --> 00:05:27.568 colleagues in which we collaborated

NOTE Confidence: 0.8114404

00:05:27.568 --> 00:05:31.014 and it was using a tracer of this

NOTE Confidence: 0.8114404

00:05:31.014 --> 00:05:32.310 nicotinic acetylcholine receptor

NOTE Confidence: 0.8114404

00:05:32.310 --> 00:05:34.514 that was competitive for Astle

NOTE Confidence: 0.8114404

00:05:34.514 --> 00:05:36.719 choline at its binding site.

NOTE Confidence: 0.8114404

00:05:36.720 --> 00:05:38.728 And now what would we expect to see

NOTE Confidence: 0.8114404

00:05:38.728 --> 00:05:40.784 if human subjects who are depressed

NOTE Confidence: 0.8114404

00:05:40.784 --> 00:05:42.644 have more Astle calling signaling

NOTE Confidence: 0.8114404

00:05:42.644 --> 00:05:44.850 when we use this competitive tracer,

NOTE Confidence: 0.8114404

00:05:44.850 --> 00:05:45.139 well,

NOTE Confidence: 0.8114404

00:05:45.139 --> 00:05:46.873 there's going to be some astral

NOTE Confidence: 0.8114404

00:05:46.873 --> 00:05:48.903 calling in the brain that binds

NOTE Confidence: 0.8114404

00:05:48.903 --> 00:05:50.367 to these nicotinic receptors,

NOTE Confidence: 0.8114404

00:05:50.370 --> 00:05:52.320 and so when that radiotracers introduced,

NOTE Confidence: 0.8114404

00:05:52.320 --> 00:05:54.330 there are going to be others

NOTE Confidence: 0.8114404

00:05:54.330 --> 00:05:56.548 binding sites that it can bind to,

NOTE Confidence: 0.8114404

00:05:56.550 --> 00:05:58.636 and we will see changes in receptor

NOTE Confidence: 0.8114404

00:05:58.636 --> 00:05:59.980 availability when this tracer

NOTE Confidence: 0.8114404

00:05:59.980 --> 00:06:00.768 is administered.

NOTE Confidence: 0.8114404

00:06:00.770 --> 00:06:02.779 How about in patients or in subjects

NOTE Confidence: 0.8114404

00:06:02.779 --> 00:06:04.999 who might have elevated Astle calling,

NOTE Confidence: 0.8114404

00:06:05.000 --> 00:06:06.328 signaling they'll have more

NOTE Confidence: 0.8114404

00:06:06.328 --> 00:06:07.656 occupancy of their receptors.

NOTE Confidence: 0.8114404

00:06:07.660 --> 00:06:09.670 And now when the tracers introduced,

NOTE Confidence: 0.8114404

00:06:09.670 --> 00:06:11.350 they'll be fewer binding sites,

NOTE Confidence: 0.8114404

00:06:11.350 --> 00:06:13.590 and that's exactly what we see in the

NOTE Confidence: 0.8114404

00:06:13.590 --> 00:06:15.698 brains of depressed human subjects.

NOTE Confidence: 0.8114404

00:06:15.700 --> 00:06:17.380 So here's just an example.

NOTE Confidence: 0.8114404

00:06:17.380 --> 00:06:19.445 Human subject has to be a non

NOTE Confidence: 0.8114404

00:06:19.445 --> 00:06:21.564 smoker because This site is also

NOTE Confidence: 0.8114404

00:06:21.564 --> 00:06:22.737 competitive with nicotine.

NOTE Confidence: 0.8515213

00:06:22.740 --> 00:06:25.062 You can see the heat map of binding and

NOTE Confidence: 0.8515213

00:06:25.062 --> 00:06:27.815 that binding is decreased in a depressed

NOTE Confidence: 0.8515213

00:06:27.815 --> 00:06:29.435 and actively depressed nonsmoker.

NOTE Confidence: 0.8515213

00:06:29.440 --> 00:06:31.555 And when we do this in a large group

NOTE Confidence: 0.8515213

00:06:31.555 --> 00:06:34.073 of human subjects you can see that

NOTE Confidence: 0.8515213

00:06:34.073 --> 00:06:36.033 that decrease in availability is

NOTE Confidence: 0.8515213

00:06:36.033 --> 00:06:38.148 obvious throughout many cortical areas,

NOTE Confidence: 0.8515213

00:06:38.150 --> 00:06:40.282 but also through deeper.

NOTE Confidence: 0.8515213

00:06:40.282 --> 00:06:41.348 Brain structures.

NOTE Confidence: 0.8515213

00:06:41.350 --> 00:06:43.198 This could also have been due

NOTE Confidence: 0.8515213

00:06:43.198 --> 00:06:44.905 to decreases in the receptor

NOTE Confidence: 0.8515213

00:06:44.905 --> 00:06:46.950 itself and not to competition,

NOTE Confidence: 0.8515213

00:06:46.950 --> 00:06:48.878 and so that we were able to do

NOTE Confidence: 0.8515213

00:06:48.878 --> 00:06:51.120 was to take postmortem human brain

NOTE Confidence: 0.8515213

00:06:51.120 --> 00:06:53.235 tissue washout Astle calling and

NOTE Confidence: 0.8515213

00:06:53.235 --> 00:06:55.588 show that there is absolutely no

NOTE Confidence: 0.8515213

00:06:55.588 --> 00:06:57.793 change in the receptor number and

NOTE Confidence: 0.8515213

00:06:57.793 --> 00:06:59.851 what our colleague Irene Esther List

NOTE Confidence: 0.8515213

00:06:59.851 --> 00:07:02.830 was able to do was to reproduce the

NOTE Confidence: 0.8515213

00:07:02.830 --> 00:07:04.710 challenge study that Janowsky did

NOTE Confidence: 0.8515213

00:07:04.780 --> 00:07:06.999 and show that in the same person

NOTE Confidence: 0.8515213

00:07:06.999 --> 00:07:09.084 who at baseline had a relatively

NOTE Confidence: 0.8515213

00:07:09.084 --> 00:07:11.352 high level of Astle choline binding.

NOTE Confidence: 0.8515213

00:07:11.360 --> 00:07:13.085 Sites available after five cystic

NOTE Confidence: 0.8515213

00:07:13.085 --> 00:07:13.775 mean administration.

NOTE Confidence: 0.8515213

00:07:13.780 --> 00:07:15.500 The number of those bindings,

NOTE Confidence: 0.8515213

00:07:15.500 --> 00:07:17.155 the availability of those binding

NOTE Confidence: 0.8515213

00:07:17.155 --> 00:07:19.585 sites goes down just as you would

NOTE Confidence: 0.8515213

00:07:19.585 --> 00:07:21.370 expect with a competitive tracer,

NOTE Confidence: 0.8515213

00:07:21.370 --> 00:07:23.521 and this is allowed us to go back and

NOTE Confidence: 0.8515213

00:07:23.521 --> 00:07:25.543 forth between mouse models in human

NOTE Confidence: 0.8515213

00:07:25.543 --> 00:07:27.268 subjects and test our hypothesis

NOTE Confidence: 0.8515213

00:07:27.324 --> 00:07:29.080 generated from these pharmacological

NOTE Confidence: 0.8515213

00:07:29.080 --> 00:07:30.836 and molecular biology experiments

NOTE Confidence: 0.8515213

00:07:30.836 --> 00:07:31.990 in human subjects.

NOTE Confidence: 0.8515213

00:07:31.990 --> 00:07:34.150 So now can we use this mass model

NOTE Confidence: 0.8515213

00:07:34.150 --> 00:07:36.180 of an anxiety and depression like

NOTE Confidence: 0.8515213

00:07:36.180 --> 00:07:38.458 state to identify sites and receptors

NOTE Confidence: 0.8515213

00:07:38.458 --> 00:07:39.997 of cholinergic signaling?

NOTE Confidence: 0.8515213

00:07:40.000 --> 00:07:41.156 Important for these behaviors?

NOTE Confidence: 0.8515213

00:07:41.156 --> 00:07:43.500 I'm going to show you just a couple

NOTE Confidence: 0.8515213

00:07:43.500 --> 00:07:44.895 slides of ongoing experiments that

NOTE Confidence: 0.8515213

00:07:44.895 --> 00:07:46.815 are not yet published to show you

NOTE Confidence: 0.8515213

00:07:46.815 --> 00:07:48.363 a flavor of what we're doing.

NOTE Confidence: 0.8515213

00:07:48.370 --> 00:07:49.534 First of all,

NOTE Confidence: 0.8515213

00:07:49.534 --> 00:07:51.862 here's a diagram of the cholinergic

NOTE Confidence: 0.8515213

00:07:51.862 --> 00:07:53.529 innervation of the hippocampus,

NOTE Confidence: 0.8515213

00:07:53.530 --> 00:07:55.695 in particular the medial septum

NOTE Confidence: 0.8515213

00:07:55.695 --> 00:07:57.860 provides a large projection to

NOTE Confidence: 0.8515213

00:07:57.932 --> 00:07:59.050 the hippocampus.

NOTE Confidence: 0.8515213

00:07:59.050 --> 00:08:01.768 And what we've been able to do is to

NOTE Confidence: 0.8515213

00:08:01.768 --> 00:08:04.026 use designer receptors exclusively

NOTE Confidence: 0.8515213

00:08:04.026 --> 00:08:07.146 access activated by designer drugs,

NOTE Confidence: 0.8515213

00:08:07.150 --> 00:08:08.898 dreads that are targeted.

NOTE Confidence: 0.8515213

00:08:08.898 --> 00:08:11.520 Only two Astle choline neurons by

NOTE Confidence: 0.8515213

00:08:11.595 --> 00:08:14.493 infusing them into mice in which a

NOTE Confidence: 0.8515213

00:08:14.493 --> 00:08:17.309 recombinase is driven by the promoter

NOTE Confidence: 0.8515213

00:08:17.309 --> 00:08:19.297 for choline acetyl transferase,

NOTE Confidence: 0.8515213

00:08:19.300 --> 00:08:22.000 the synthetic enzyme for astral cooling,

NOTE Confidence: 0.8515213

00:08:22.000 --> 00:08:24.622 and to then direct these dreads

NOTE Confidence: 0.8515213

00:08:24.622 --> 00:08:26.939 locali to the hippocampus by

NOTE Confidence: 0.8515213

00:08:26.939 --> 00:08:29.369 infusing them into the hippocampus.

NOTE Confidence: 0.8515213

00:08:29.370 --> 00:08:31.506 Packaged in a virus that infects

NOTE Confidence: 0.8515213

00:08:31.506 --> 00:08:33.323 terminals of neurons and goes

NOTE Confidence: 0.8515213

00:08:33.323 --> 00:08:34.938 back to their cell bodies.

NOTE Confidence: 0.8515213

00:08:34.940 --> 00:08:37.028 So what does that look like?

NOTE Confidence: 0.8515213

00:08:37.030 --> 00:08:38.765 We infuse the retrograde dread

NOTE Confidence: 0.8515213

00:08:38.765 --> 00:08:40.153 here into the hippocampus.

NOTE Confidence: 0.8515213

00:08:40.160 --> 00:08:42.589 It goes back to the medial septum,

NOTE Confidence: 0.8515213

00:08:42.590 --> 00:08:44.942 and now when we give the chemical

NOTE Confidence: 0.8515213

00:08:44.942 --> 00:08:46.420 activator of this dread,

NOTE Confidence: 0.8515213

00:08:46.420 --> 00:08:48.180 we can exclusively activate this

NOTE Confidence: 0.8515213

00:08:48.180 --> 00:08:50.250 pathway in the brain and ask,

NOTE Confidence: 0.8515213

00:08:50.250 --> 00:08:51.985 does that also change behavior

NOTE Confidence: 0.8515213

00:08:51.985 --> 00:08:53.373 in ways relevant distress?

NOTE Confidence: 0.8515213

00:08:53.380 --> 00:08:55.788 And that's exactly what we see in a

NOTE Confidence: 0.8515213

00:08:55.788 --> 00:08:58.598 number of tests that I'm diagramming here.

NOTE Confidence: 0.8515213

00:08:58.600 --> 00:09:00.020 The light dark box,

NOTE Confidence: 0.8515213

00:09:00.020 --> 00:09:01.795 which is sensitive to anxiolytic

NOTE Confidence: 0.8515213

00:09:01.795 --> 00:09:02.490 medications that.

NOTE Confidence: 0.8515213

00:09:02.490 --> 00:09:04.758 Forced women tail suspension tests that

NOTE Confidence: 0.8515213

00:09:04.758 --> 00:09:06.741 are sensitive to acute administration

NOTE Confidence: 0.8515213

00:09:06.741 --> 00:09:09.189 of anti depressants and the social

NOTE Confidence: 0.8515213

00:09:09.189 --> 00:09:11.997 defeat test which is sensitive to

NOTE Confidence: 0.8515213

00:09:11.997 --> 00:09:14.017 chronic administration of antidepressants.

NOTE Confidence: 0.8515213

00:09:14.020 --> 00:09:15.970 All show changes in behavior

NOTE Confidence: 0.8515213

00:09:15.970 --> 00:09:17.920 when this dread activates the

NOTE Confidence: 0.8515213

00:09:17.995 --> 00:09:20.420 hippocampus that choline the astral.

NOTE Confidence: 0.8515213

00:09:20.420 --> 00:09:22.490 Colleen inputs to the big campus

NOTE Confidence: 0.8515213

00:09:22.490 --> 00:09:24.807 that are relevant that are consistent

NOTE Confidence: 0.8515213

00:09:24.807 --> 00:09:26.972 with the idea that increased

NOTE Confidence: 0.8515213

00:09:26.972 --> 00:09:28.924 hippocampal Estel cooling system

NOTE Confidence: 0.8515213

00:09:28.924 --> 00:09:30.667 signaling increases behaviors.

NOTE Confidence: 0.8276835

00:09:30.670 --> 00:09:33.418 Relevant distress, and we've now done.

NOTE Confidence: 0.8276835

00:09:33.420 --> 00:09:37.308 A number of experiments to show that this is

NOTE Confidence: 0.8276835

00:09:37.308 --> 00:09:40.758 actually mediated by Astle choline, not Co.

NOTE Confidence: 0.8276835

00:09:40.758 --> 00:09:42.803 Released neurotransmitters because if we

NOTE Confidence: 0.8276835

00:09:42.803 --> 00:09:45.193 locally infused and nicotinic antagonist

NOTE Confidence: 0.8276835

00:09:45.193 --> 00:09:47.397 mecamylamine into the hippocampus,

NOTE Confidence: 0.8276835

00:09:47.400 --> 00:09:51.128 we can reverse these effects of the dread.

NOTE Confidence: 0.8276835

00:09:51.130 --> 00:09:53.600 So here's the control plus

NOTE Confidence: 0.8276835

00:09:53.600 --> 00:09:56.070 Mecamylamine compared to the Dread

NOTE Confidence: 0.8276835

00:09:56.160 --> 00:09:59.080 activation in three different tests.

NOTE Confidence: 0.8276835

00:09:59.080 --> 00:10:01.068 So that means that.

NOTE Confidence: 0.8276835

00:10:01.070 --> 00:10:03.206 We can actually increase Astle calling

NOTE Confidence: 0.8276835

00:10:03.206 --> 00:10:05.861 signaling using this thread and reverse it

NOTE Confidence: 0.8276835

00:10:05.861 --> 00:10:07.816 using a nicotinic acetylcholine antagonist.

NOTE Confidence: 0.8276835

00:10:07.820 --> 00:10:10.412 So we have a number of studies that

NOTE Confidence: 0.8276835

00:10:10.412 --> 00:10:12.335 are dissecting the signaling of

NOTE Confidence: 0.8276835

00:10:12.335 --> 00:10:14.345 Astle calling in brain structures

NOTE Confidence: 0.8276835

00:10:14.345 --> 00:10:16.450 in addition to the hippocampus.

NOTE Confidence: 0.8276835

00:10:16.450 --> 00:10:17.946 For example, the amygdala,

NOTE Confidence: 0.8276835

00:10:17.946 --> 00:10:19.068 the prefrontal cortex,

NOTE Confidence: 0.8276835

00:10:19.070 --> 00:10:21.218 and then locally the basil forebrain

NOTE Confidence: 0.8276835

00:10:21.218 --> 00:10:23.496 complex where the cell bodies of

NOTE Confidence: 0.8276835

00:10:23.496 --> 00:10:25.446 those Astle calling neurons reside,

NOTE Confidence: 0.8276835

00:10:25.450 --> 00:10:27.664 and altogether what we are building

NOTE Confidence: 0.8276835

00:10:27.664 --> 00:10:30.371 is an integrated picture of how Astle

NOTE Confidence: 0.8276835

00:10:30.371 --> 00:10:32.311 calling signaling sets the threshold

NOTE Confidence: 0.8276835

00:10:32.311 --> 00:10:34.320 for behaviors relevant to stress.

NOTE Confidence: 0.8276835

00:10:34.320 --> 00:10:36.378 In mice and how we might translate

NOTE Confidence: 0.8276835

00:10:36.378 --> 00:10:38.307 those to understanding how I still

NOTE Confidence: 0.8276835

00:10:38.307 --> 00:10:39.627 calling signaling is affecting

NOTE Confidence: 0.8276835

00:10:39.627 --> 00:10:41.449 behavior in depressed human subjects,

NOTE Confidence: 0.8276835

00:10:41.450 --> 00:10:43.767 I want to thank the lab members

NOTE Confidence: 0.8276835

00:10:43.767 --> 00:10:45.659 who are contributing to this work.

NOTE Confidence: 0.8276835

00:10:45.660 --> 00:10:47.340 Particularly young men are a

NOTE Confidence: 0.8276835

00:10:47.340 --> 00:10:49.380 research scientist in the lab who's

NOTE Confidence: 0.8276835

00:10:49.380 --> 00:10:51.168 worked with me for many years.

NOTE Confidence: 0.8276835

00:10:51.170 --> 00:10:52.790 Thank you everybody for listening.

NOTE Confidence: 0.8276835

00:10:52.790 --> 00:10:54.082 I really enjoyed presenting

NOTE Confidence: 0.8276835

00:10:54.082 --> 00:10:55.697 this glimpse of the work.

NOTE Confidence: 0.8276835

00:10:55.700 --> 00:10:57.740 Please contact me if you'd

NOTE Confidence: 0.8276835

00:10:57.740 --> 00:10:59.372 like more information about

NOTE Confidence: 0.8276835

00:10:59.372 --> 00:11:01.550 the work going on in my lap.

NOTE Confidence: 0.8276835

00:11:01.550 --> 00:11:01.970 Bye bye.