WEBVTT

NOTE duration:"00:48:00.2800000"

NOTE recognizability:0.529

NOTE language:en-us

NOTE Confidence: 0.71403414

00:00:00.000 --> 00:00:00.880 OK.

NOTE Confidence: 0.71403414

00:00:05.480 --> 00:00:06.240 Yeah. Thank you so much,

NOTE Confidence: 0.71403414

00:00:06.240 --> 00:00:09.400 Jerry, for the introduction.

NOTE Confidence: 0.71403414

00:00:09.400 --> 00:00:12.048 And this work with Anglo 5 I've been

NOTE Confidence: 0.71403414

00:00:12.048 --> 00:00:14.439 doing for I think about 15 years.

NOTE Confidence: 0.71403414

00:00:14.440 --> 00:00:16.190 And it actually started in

NOTE Confidence: 0.71403414

00:00:16.190 --> 00:00:17.240 collaboration with Jerry.

NOTE Confidence: 0.71403414

00:00:17.240 --> 00:00:19.892 Jerry was my mentor on my

NOTE Confidence: 0.71403414

00:00:19.892 --> 00:00:22.200 first imaging study with this.

NOTE Confidence: 0.71403414

00:00:22.200 --> 00:00:24.288 I will not be talking about

NOTE Confidence: 0.71403414

00:00:24.288 --> 00:00:25.680 synaptic density much today,

NOTE Confidence: 0.71403414

00:00:25.680 --> 00:00:29.170 but I'd be happy to come back and another

NOTE Confidence: 0.71403414

00:00:29.170 --> 00:00:31.960 grand rounds and talk about that.

NOTE Confidence: 0.71403414

00:00:31.960 --> 00:00:34.655 So if you guys know it takes

NOTE Confidence: 0.71403414

00:00:34.655 --> 00:00:37.199 an army to do this work,

NOTE Confidence: 0.71403414

00:00:37.200 --> 00:00:38.887 this is some of the army that

NOTE Confidence: 0.71403414

00:00:38.887 --> 00:00:40.399 has helped me do this work.

NOTE Confidence: 0.71403414

00:00:40.400 --> 00:00:43.001 And I just want to just show all the

NOTE Confidence: 0.71403414

00:00:43.001 --> 00:00:45.437 people now in case we run out of time.

NOTE Confidence: 0.71403414

00:00:45.440 --> 00:00:47.555 And these are the acknowledgements

NOTE Confidence: 0.71403414

00:00:47.555 --> 00:00:49.670 on the translational brain imaging

NOTE Confidence: 0.71403414

00:00:49.731 --> 00:00:52.764 program with Nicole de La Jolla and

NOTE Confidence: 0.71403414

00:00:52.764 --> 00:00:55.288 Sarah Davanni have been doing a lot

NOTE Confidence: 0.71403414

00:00:55.288 --> 00:00:57.325 of help with recruitment of subjects

NOTE Confidence: 0.71403414

00:00:57.325 --> 00:00:58.673 and identification of subjects.

NOTE Confidence: 0.71403414

00:00:58.680 --> 00:01:00.990 And then Rich Carson has been my

NOTE Confidence: 0.71403414

00:01:00.990 --> 00:01:03.318 mentor from when I started doing PET.

NOTE Confidence: 0.71403414

00:01:03.320 --> 00:01:04.580 And then Chrissy de Lorenzo

NOTE Confidence: 0.71403414

00:01:04.580 --> 00:01:06.154 has done a lot of ketamine.

NOTE Confidence: 0.71403414

00:01:06.154 --> 00:01:09.147 I'm go 5 work with me and Jane Taylor,

NOTE Confidence: 0.71403414

00:01:09.147 --> 00:01:10.992 Hilary Bloomberg and Jerry Sinacor

NOTE Confidence: 0.71403414

00:01:10.992 --> 00:01:12.957 have really helped a lot through

NOTE Confidence: 0.71403414

00:01:12.960 --> 00:01:15.760 for clinical and clinical studies.

NOTE Confidence: 0.71403414

00:01:15.760 --> 00:01:19.000 And I don't have any relevant

NOTE Confidence: 0.71403414

00:01:19.000 --> 00:01:20.080 financial disclosures.

NOTE Confidence: 0.71403414

00:01:20.080 --> 00:01:22.888 And so why did I decide to study

NOTE Confidence: 0.71403414

00:01:22.888 --> 00:01:25.318 glutamate besides the fact that we

NOTE Confidence: 0.71403414

00:01:25.318 --> 00:01:26.974 can actually image glutamatergic

NOTE Confidence: 0.71403414

00:01:26.974 --> 00:01:29.279 system in the brain in humans?

NOTE Confidence: 0.71403414

00:01:29.280 --> 00:01:29.644 Well,

NOTE Confidence: 0.71403414

00:01:29.644 --> 00:01:31.464 glutamate is the most common

NOTE Confidence: 0.71403414

00:01:31.464 --> 00:01:33.650 neurotransmitter in the brain with 80

NOTE Confidence: 0.71403414

00:01:33.650 --> 00:01:35.840 to 90% of synapses being glutamatergic.

NOTE Confidence: 0.71403414

00:01:35.840 --> 00:01:37.800 And so if you think about it,

NOTE Confidence: 0.71403414

00:01:37.800 --> 00:01:39.660 whatever system you're studying,

NOTE Confidence: 0.71403414

00:01:39.660 --> 00:01:41.520 whatever disorder you're studying,

NOTE Confidence: 0.71403414

00:01:41.520 --> 00:01:43.260 glutamate dysfunction is going to

NOTE Confidence: 0.71403414

00:01:43.260 --> 00:01:45.000 be implicated in that disorder.

NOTE Confidence: 0.71403414

00:01:45.000 --> 00:01:47.838 There are two types of receptors.

NOTE Confidence: 0.71403414

00:01:47.840 --> 00:01:50.040 Bionotropic receptors are responsible

NOTE Confidence: 0.71403414

00:01:50.040 --> 00:01:52.240 for fast excitatory transmission.

NOTE Confidence: 0.71403414

00:01:52.240 --> 00:01:54.365 Emmetabotropic have more of a

NOTE Confidence: 0.71403414

00:01:54.365 --> 00:01:57.063 modulatory role in the central nervous

NOTE Confidence: 0.71403414

00:01:57.063 --> 00:01:59.918 system and so I'm studying Amglu 5.

NOTE Confidence: 0.71403414

00:01:59.920 --> 00:02:02.320 It's AG protein coupled receptor.

NOTE Confidence: 0.71403414

00:02:02.320 --> 00:02:04.255 It is located mostly post

NOTE Confidence: 0.71403414

00:02:04.255 --> 00:02:05.803 synaptically everywhere in the

NOTE Confidence: 0.71403414

00:02:05.803 --> 00:02:07.880 brain and the peripheral tissue.

NOTE Confidence: 0.71403414

00:02:07.880 --> 00:02:09.440 It is involved in everything that

NOTE Confidence: 0.71403414

00:02:09.440 --> 00:02:10.900 we do including learning, memory,

NOTE Confidence: 0.71403414

00:02:10.900 --> 00:02:13.000 anxiety and perception of pain.

NOTE Confidence: 0.71403414

00:02:13.000 --> 00:02:16.048 Probably sleeping cycle as well and

NOTE Confidence: 0.71403414

00:02:16.048 --> 00:02:18.088 allosteric modulation of the system

NOTE Confidence: 0.71403414

00:02:18.088 --> 00:02:19.720 contributes to cognitive function,

NOTE Confidence: 0.71403414

00:02:19.720 --> 00:02:20.334 anxiety, pain.

NOTE Confidence: 0.71403414

00:02:20.334 --> 00:02:23.178 A lot of this work has been done in

NOTE Confidence: 0.71403414

00:02:23.178 --> 00:02:25.418 animal models and then I'll show you

NOTE Confidence: 0.71403414

00:02:25.418 --> 00:02:27.756 some work that we've done in human.

NOTE Confidence: 0.71403414

00:02:27.760 --> 00:02:30.424 And so the way I study Anglo 5 is

NOTE Confidence: 0.71403414

00:02:30.424 --> 00:02:33.360 through positron emission tomography or PET.

NOTE Confidence: 0.71403414

00:02:33.360 --> 00:02:36.304 I'll just show you a few slides on

NOTE Confidence: 0.71403414

00:02:36.304 --> 00:02:38.740 what we actually study and how PET

NOTE Confidence: 0.71403414

00:02:38.740 --> 00:02:41.000 works so that you can understand better

NOTE Confidence: 0.71403414

00:02:41.000 --> 00:02:42.960 what it is that I'm studying and

NOTE Confidence: 0.71403414

00:02:42.960 --> 00:02:44.956 the data that I will show you later.

NOTE Confidence: 0.71403414

00:02:44.960 --> 00:02:46.560 And so for PET, we need a cyclotron,

NOTE Confidence: 0.71403414

00:02:46.560 --> 00:02:48.822 which is a large machine that

NOTE Confidence: 0.71403414

00:02:48.822 --> 00:02:50.406 makes radioactive particles such

NOTE Confidence: 0.71403414

00:02:50.406 --> 00:02:52.636 as carbon 11 and F18,

NOTE Confidence: 0.71403414

00:02:52.640 --> 00:02:55.624 which we then bind to whatever target

NOTE Confidence: 0.71403414

00:02:55.624 --> 00:02:57.752 you're sending into the brain to bind

NOTE Confidence: 0.71403414

00:02:57.752 --> 00:03:00.399 to the enzyme neurotransmitter receptor,

NOTE Confidence: 0.71403414

00:03:00.400 --> 00:03:02.598 whatever it is you're trying to study.

NOTE Confidence: 0.71403414

00:03:02.600 --> 00:03:05.000 And this composite is called the

NOTE Confidence: 0.71403414

00:03:05.000 --> 00:03:06.640 radio pharmaceutical or radio

NOTE Confidence: 0.71403414

00:03:06.640 --> 00:03:08.320 ligand or radio tracer.

NOTE Confidence: 0.71403414

00:03:08.320 --> 00:03:11.000 We use those terms interchangeably.

NOTE Confidence: 0.71403414

00:03:11.000 --> 00:03:12.835 I also short and sometimes

NOTE Confidence: 0.71403414

00:03:12.835 --> 00:03:14.670 I'll say ligand or tracer

NOTE Confidence: 0.62159127

00:03:14.741 --> 00:03:16.995 and it all means the same thing.

NOTE Confidence: 0.62159127

00:03:17.000 --> 00:03:19.247 We inject this into the subject as

NOTE Confidence: 0.62159127

00:03:19.247 --> 00:03:21.723 a bolus over a one minute push or

NOTE Confidence: 0.62159127

00:03:21.723 --> 00:03:23.421 bolus plus injection over could be

NOTE Confidence: 0.62159127

00:03:23.421 --> 00:03:25.379 an hour a couple hours depending

NOTE Confidence: 0.62159127

00:03:25.379 --> 00:03:27.748 on the system that we're studying.

NOTE Confidence: 0.62159127

00:03:27.748 --> 00:03:29.833 And then we acquire images.

NOTE Confidence: 0.62159127

00:03:29.840 --> 00:03:32.640 And this is just an example of a PET scanner.

NOTE Confidence: 0.62159127

00:03:32.640 --> 00:03:33.880 This is an outdated picture,

NOTE Confidence: 0.62159127

00:03:33.880 --> 00:03:36.877 but it gives you an idea of a brain.

NOTE Confidence: 0.62159127

00:03:36.880 --> 00:03:39.484 Dedicated PET scanner has a short

NOTE Confidence: 0.62159127

00:03:39.484 --> 00:03:41.860 bore where only the subject's head

NOTE Confidence: 0.62159127

00:03:41.860 --> 00:03:44.315 is positioned and so people with

NOTE Confidence: 0.62159127

00:03:44.315 --> 00:03:46.550 claustrophobia really have an easier

NOTE Confidence: 0.62159127

00:03:46.550 --> 00:03:48.384 time participating in PET scans.

NOTE Confidence: 0.62159127

00:03:48.384 --> 00:03:50.114 Now we have different scanners

NOTE Confidence: 0.62159127

00:03:50.114 --> 00:03:52.131 with where the bore is larger and

NOTE Confidence: 0.62159127

00:03:52.131 --> 00:03:53.760 the whole body needs to go in.

NOTE Confidence: 0.62159127

00:03:53.760 --> 00:03:56.640 So we do account for claustrophobia.

NOTE Confidence: 0.62159127

00:03:56.640 --> 00:03:58.280 And so as Jerry mentioned,

NOTE Confidence: 0.62159127

00:03:58.280 --> 00:04:01.600 I'm a neuropsychologist by training.

NOTE Confidence: 0.62159127

00:04:01.600 --> 00:04:03.920 And so for me when I found PET,

NOTE Confidence: 0.62159127

00:04:03.920 --> 00:04:06.512 I was super excited.

NOTE Confidence: 0.62159127

00:04:06.512 --> 00:04:08.618 And I'm really honoured to be able

NOTE Confidence: 0.62159127

00:04:08.618 --> 00:04:10.459 to do these studies where I can look

NOTE Confidence: 0.62159127

00:04:10.459 --> 00:04:12.165 at what's going on in the brain and

NOTE Confidence: 0.62159127

00:04:12.165 --> 00:04:13.877 I can ask people how do they feel,

NOTE Confidence: 0.62159127

00:04:13.880 --> 00:04:15.560 measure their cognition, etcetera, etcetera.

NOTE Confidence: 0.62159127

00:04:15.560 --> 00:04:17.000 So I can, you know,

NOTE Confidence: 0.62159127

00:04:17.000 --> 00:04:21.480 unite the human and neuroscience.

NOTE Confidence: 0.62159127

00:04:21.480 --> 00:04:24.301 And so this is an example of

NOTE Confidence: 0.62159127

00:04:24.301 --> 00:04:27.160 participation in the study by a subject.

NOTE Confidence: 0.62159127

00:04:27.160 --> 00:04:29.338 So first we collect MRI images

NOTE Confidence: 0.62159127

00:04:29.338 --> 00:04:31.237 to guide placements of regions

NOTE Confidence: 0.62159127

00:04:31.237 --> 00:04:33.695 of interest for PET and to make

NOTE Confidence: 0.62159127

00:04:33.695 --> 00:04:35.320 sure there are no abnormalities.

NOTE Confidence: 0.62159127

00:04:35.320 --> 00:04:37.624 Sometimes we see people have tumors

NOTE Confidence: 0.62159127

00:04:37.624 --> 00:04:40.317 or hemorrhage and we of course report

NOTE Confidence: 0.62159127

00:04:40.317 --> 00:04:42.695 that and then the radio chemist

NOTE Confidence: 0.62159127

00:04:42.695 --> 00:04:45.103 synthesize the radio tracer when the

NOTE Confidence: 0.62159127

00:04:45.103 --> 00:04:47.315 subjects show up at the PET scan.

NOTE Confidence: 0.62159127

00:04:47.320 --> 00:04:48.657 So it is not something that we

NOTE Confidence: 0.62159127

00:04:48.657 --> 00:04:49.639 can do ahead of time.

NOTE Confidence: 0.62159127

00:04:49.640 --> 00:04:53.000 The radio tracers have a half

NOTE Confidence: 0.62159127

00:04:53.000 --> 00:04:54.360 life of some 20 minutes,

NOTE Confidence: 0.62159127

00:04:54.360 --> 00:04:55.341 some 110 minutes.

NOTE Confidence: 0.62159127

00:04:55.341 --> 00:04:57.630 And so it's not something that can

NOTE Confidence: 0.62159127

00:04:57.697 --> 00:04:59.809 be done in batches and distributed

NOTE Confidence: 0.62159127

00:04:59.809 --> 00:05:01.600 throughout the day or week.

NOTE Confidence: 0.62159127

00:05:01.600 --> 00:05:04.183 And then we collect bloods for metabolism

NOTE Confidence: 0.62159127

00:05:04.183 --> 00:05:06.558 and protein binding of the radio tracer.

NOTE Confidence: 0.62159127

00:05:06.560 --> 00:05:08.200 Since everybody you know works,

NOTE Confidence: 0.62159127

00:05:08.200 --> 00:05:09.888 their systems work differently.

NOTE Confidence: 0.62159127

00:05:09.888 --> 00:05:12.420 And then we inject the radio

NOTE Confidence: 0.62159127

00:05:12.490 --> 00:05:14.600 tracer and collect PET images.

NOTE Confidence: 0.62159127

00:05:14.600 --> 00:05:17.295 And so this is an example of

NOTE Confidence: 0.62159127

00:05:17.295 --> 00:05:20.000 a PET image and Amar image.

NOTE Confidence: 0.62159127

00:05:20.000 --> 00:05:23.320 And so for pet outcome measures we have,

NOTE Confidence: 0.62159127

00:05:23.320 --> 00:05:24.331 we have several,

NOTE Confidence: 0.62159127

00:05:24.331 --> 00:05:26.353 but I'll be talking about two.

NOTE Confidence: 0.62159127

00:05:26.360 --> 00:05:29.440 One is BPNT, which is a binding potential.

NOTE Confidence: 0.62159127

00:05:29.440 --> 00:05:31.414 It's how much radioactivity we have in

NOTE Confidence: 0.62159127

00:05:31.414 --> 00:05:33.519 a region that you're trying to study

NOTE Confidence: 0.62159127

00:05:33.520 --> 00:05:35.422 versus how much radioactivity is in

NOTE Confidence: 0.62159127

00:05:35.422 --> 00:05:37.617 the region that has nothing of what

NOTE Confidence: 0.62159127

00:05:37.617 --> 00:05:39.633 it is that you're trying to study.

NOTE Confidence: 0.62159127

00:05:39.640 --> 00:05:42.436 So it has negligible specific binding.

NOTE Confidence: 0.62159127

00:05:42.440 --> 00:05:43.812 Sometimes for some systems,

NOTE Confidence: 0.62159127

00:05:43.812 --> 00:05:46.264 we don't have that and so we

NOTE Confidence: 0.62159127

00:05:46.264 --> 00:05:47.560 have to measure blood.

NOTE Confidence: 0.62159127

00:05:47.560 --> 00:05:49.814 And so we look at how much

NOTE Confidence: 0.62159127

00:05:49.814 --> 00:05:52.220 radioactivity is in the brain and the

NOTE Confidence: 0.62159127

00:05:52.220 --> 00:05:54.440 tissue that you're trying to study

NOTE Confidence: 0.62159127

00:05:54.440 --> 00:05:56.718 versus how much is in the blood.

NOTE Confidence: 0.62159127

00:05:56.720 --> 00:05:58.560 And so the first one is called BPNT

NOTE Confidence: 0.62159127

00:05:58.560 --> 00:06:00.360 and the second one is called BT.

NOTE Confidence: 0.62159127

00:06:00.360 --> 00:06:01.836 And I as I go through,

NOTE Confidence: 0.62159127

00:06:01.840 --> 00:06:03.200 I will tell you which one I used.

NOTE Confidence: 0.5679808

00:06:05.240 --> 00:06:08.468 We have two radio ligands that most

NOTE Confidence: 0.5679808

00:06:08.468 --> 00:06:11.432 commonly used to study Onglu 5 in human

NOTE Confidence: 0.5679808

00:06:11.432 --> 00:06:14.520 in vivo and I have used both of these.

NOTE Confidence: 0.5679808

00:06:14.520 --> 00:06:17.224 One is F18 FPEB, it has very high

NOTE Confidence: 0.5679808

00:06:17.224 --> 00:06:19.377 affinity and specificity for the

NOTE Confidence: 0.5679808

00:06:19.377 --> 00:06:21.717 receptor has slower kinetics of

NOTE Confidence: 0.5679808

00:06:21.720 --> 00:06:25.462 110 minute half life and and that

NOTE Confidence: 0.5679808

00:06:25.462 --> 00:06:27.317 sorry half life's 110 minutes.

NOTE Confidence: 0.5679808

00:06:27.320 --> 00:06:29.609 And we think because of its high

NOTE Confidence: 0.5679808

00:06:29.609 --> 00:06:31.039 specificity it's well suited

NOTE Confidence: 0.5679808

00:06:31.039 --> 00:06:32.959 to study between group changes.

NOTE Confidence: 0.5679808

00:06:32.960 --> 00:06:34.664 So even if the differences between

NOTE Confidence: 0.5679808

00:06:34.664 --> 00:06:36.370 groups are really, really small,

NOTE Confidence: 0.5679808

00:06:36.370 --> 00:06:38.920 we can detect it with FBEB.

NOTE Confidence: 0.5679808

00:06:38.920 --> 00:06:40.600 AEP 688 is also high affinity,

NOTE Confidence: 0.5679808

00:06:40.600 --> 00:06:42.840 not as good as FBEB but because

NOTE Confidence: 0.5679808

00:06:42.840 --> 00:06:44.920 of its short half life we can do

NOTE Confidence: 0.5679808

00:06:44.979 --> 00:06:46.629 challenge studies on the same

NOTE Confidence: 0.5679808

00:06:46.629 --> 00:06:48.701 day we can administer this radio

NOTE Confidence: 0.5679808

00:06:48.701 --> 00:06:50.117 tracer even three times.

NOTE Confidence: 0.5679808

00:06:50.120 --> 00:06:52.960 They're both negative ballasteric modulators,

NOTE Confidence: 0.5679808

00:06:52.960 --> 00:06:55.067 which means they bind on the receptor

NOTE Confidence: 0.5679808

00:06:55.067 --> 00:06:58.347 on a site different from where they're

NOTE Confidence: 0.5679808

00:06:58.347 --> 00:07:00.078 endogenous neurotransmitter binds.

NOTE Confidence: 0.5679808

00:07:00.080 --> 00:07:02.160 And I will explain that to you in a minute.

NOTE Confidence: 0.56170344

00:07:04.400 --> 00:07:06.290 So first I wanted to show you

NOTE Confidence: 0.56170344

00:07:06.290 --> 00:07:08.104 what typically happens in the

NOTE Confidence: 0.56170344

00:07:08.104 --> 00:07:10.034 brain when we measure receptors,

NOTE Confidence: 0.56170344

00:07:10.040 --> 00:07:12.026 and then I will show you

NOTE Confidence: 0.56170344

00:07:12.026 --> 00:07:13.560 what happens with Anglo 5.

NOTE Confidence: 0.56170344

00:07:13.560 --> 00:07:16.479 So this was published by Mark Laurel,

NOTE Confidence: 0.56170344

00:07:16.480 --> 00:07:20.228 who was a trainee here a few decades ago.

NOTE Confidence: 0.56170344

00:07:20.228 --> 00:07:23.118 Then he was here again for a few months,

NOTE Confidence: 0.56170344

00:07:23.120 --> 00:07:25.493 maybe a decade ago, and he explained

NOTE Confidence: 0.56170344

00:07:25.493 --> 00:07:28.280 really well the classical occupancy model.

NOTE Confidence: 0.56170344

00:07:28.280 --> 00:07:31.840 So the gap, the little Y shapes are,

NOTE Confidence: 0.56170344

00:07:31.840 --> 00:07:34.960 for example, D2 dopamine receptors,

NOTE Confidence: 0.56170344

00:07:34.960 --> 00:07:38.600 the the black triangles is dopamine,

NOTE Confidence: 0.56170344

00:07:38.600 --> 00:07:40.658 the endogenous neurotransmitter

NOTE Confidence: 0.56170344

00:07:40.658 --> 00:07:42.716 or endogenous ligand,

NOTE Confidence: 0.56170344

00:07:42.720 --> 00:07:45.156 and the Pentagon shapes are rocklopride,

NOTE Confidence: 0.56170344

00:07:45.160 --> 00:07:46.456 our radio tracer.

NOTE Confidence: 0.56170344

00:07:46.456 --> 00:07:48.616 So in the typical situation

NOTE Confidence: 0.56170344

00:07:48.616 --> 00:07:50.559 in the middle here,

NOTE Confidence: 0.56170344

00:07:50.560 --> 00:07:52.275 some of the receptors are going to

NOTE Confidence: 0.56170344

00:07:52.275 --> 00:07:54.178 be occupied by dopamine, not all.

NOTE Confidence: 0.56170344

00:07:54.178 --> 00:07:56.152 And so the radio ligand can

NOTE Confidence: 0.56170344

00:07:56.152 --> 00:07:58.000 occupy the other receptors.

NOTE Confidence: 0.56170344

00:07:58.000 --> 00:08:01.042 So the endogenous neurotransmitter has higher

NOTE Confidence: 0.56170344

00:08:01.042 --> 00:08:04.124 affinity or higher ligand for the receptor,

NOTE Confidence: 0.56170344

00:08:04.124 --> 00:08:06.420 so it's going to the radio

NOTE Confidence: 0.56170344

00:08:06.420 --> 00:08:08.320 ligand cannot kick them off.

NOTE Confidence: 0.56170344

00:08:08.320 --> 00:08:09.950 So whatever dopamine does not

NOTE Confidence: 0.56170344

00:08:09.950 --> 00:08:12.040 occupy is what rectified can occupy.

NOTE Confidence: 0.56170344

00:08:12.040 --> 00:08:15.316 And so this is called receptor availability.

NOTE Confidence: 0.56170344

00:08:15.320 --> 00:08:17.078 When we have a situation where

NOTE Confidence: 0.56170344

00:08:17.078 --> 00:08:18.880 we have too much dopamine,

NOTE Confidence: 0.56170344

00:08:18.880 --> 00:08:19.616 for example,

NOTE Confidence: 0.56170344

00:08:19.616 --> 00:08:20.720 we gave subjects

NOTE Confidence: 0.67398137

00:08:22.800 --> 00:08:24.800 a medication that induces dopamine

NOTE Confidence: 0.67398137

00:08:24.800 --> 00:08:27.544 relief or a dopamine release or we have a

NOTE Confidence: 0.67398137

00:08:27.544 --> 00:08:29.718 condition where there's too much dopamine,

NOTE Confidence: 0.67398137

00:08:29.720 --> 00:08:31.664 we don't have as many receptors

NOTE Confidence: 0.67398137

00:08:31.664 --> 00:08:33.440 for the radioligand to occupy.

NOTE Confidence: 0.67398137

00:08:33.440 --> 00:08:35.060 So now we're measuring

NOTE Confidence: 0.67398137

00:08:35.060 --> 00:08:36.275 low receptor availability.

NOTE Confidence: 0.67398137

00:08:36.280 --> 00:08:37.954 And then on the left here is the opposite.

NOTE Confidence: 0.67398137

00:08:37.960 --> 00:08:39.468 When there's either dopamine

NOTE Confidence: 0.67398137

00:08:39.468 --> 00:08:41.730 depletion by tryptophan or a situation

NOTE Confidence: 0.67398137

00:08:41.791 --> 00:08:43.741 where the subject has too little

NOTE Confidence: 0.67398137

00:08:43.741 --> 00:08:45.554 dopamine because of an illness,

NOTE Confidence: 0.67398137

00:08:45.554 --> 00:08:47.639 we have more receptors available

NOTE Confidence: 0.67398137

00:08:47.639 --> 00:08:49.950 and so high receptor availability

NOTE Confidence: 0.67398137

00:08:49.950 --> 00:08:52.400 is going to be measured.

NOTE Confidence: 0.67398137

00:08:52.400 --> 00:08:54.160 Unfortunately, in my case,

NOTE Confidence: 0.67398137

00:08:54.160 --> 00:08:56.800 Anglu 5 works a bit differently.

NOTE Confidence: 0.67398137

00:08:56.800 --> 00:09:00.552 So the endogenous ligand glutamate is

NOTE Confidence: 0.67398137

00:09:00.552 --> 00:09:03.520 going to bind in the extrasynaptic space,

NOTE Confidence: 0.67398137

00:09:03.520 --> 00:09:05.950 but the radioligand binds in

NOTE Confidence: 0.67398137

00:09:05.950 --> 00:09:07.464 the membrane space.

NOTE Confidence: 0.67398137

00:09:07.464 --> 00:09:10.024 So there's no direct competition

NOTE Confidence: 0.67398137

00:09:10.024 --> 00:09:13.150 between the endogenous ligand and the

NOTE Confidence: 0.67398137

00:09:13.150 --> 00:09:16.239 neurotransmitter and the radio ligand.

NOTE Confidence: 0.67398137

00:09:16.240 --> 00:09:19.474 So whatever happens at the glutamate site

NOTE Confidence: 0.67398137

00:09:19.480 --> 00:09:23.638 may not influence the radio ligand site.

NOTE Confidence: 0.67398137

00:09:23.640 --> 00:09:26.125 And I was really trying hard to

NOTE Confidence: 0.67398137

00:09:26.125 --> 00:09:28.249 understand that concept and some other

NOTE Confidence: 0.67398137

00:09:28.249 --> 00:09:30.552 concepts that I will show you later.

NOTE Confidence: 0.67398137

00:09:30.560 --> 00:09:32.600 And at the same time I was doing my In

NOTE Confidence: 0.67398137

00:09:32.661 --> 00:09:35.344 Vivo work, Jonathan Jovic at Columbia,

NOTE Confidence: 0.67398137

00:09:35.344 --> 00:09:39.594 I was doing some hexel work showing these

NOTE Confidence: 0.67398137

00:09:39.594 --> 00:09:42.179 similar phenomenon and explaining how

NOTE Confidence: 0.67398137

00:09:42.179 --> 00:09:45.437 Anglo 5 ligands really work in brain.

NOTE Confidence: 0.67398137

00:09:45.440 --> 00:09:50.784 So in one study he administered glutamate

NOTE Confidence: 0.67398137

00:09:50.784 --> 00:09:53.536 and he saw that it did not influence

NOTE Confidence: 0.67398137

00:09:53.536 --> 00:09:56.435 the binding of the radioligand so again,

NOTE Confidence: 0.67398137

00:09:56.440 --> 00:09:57.280 as I showed you before,

NOTE Confidence: 0.67398137

00:09:57.280 --> 00:09:58.932 there's no drug competition

NOTE Confidence: 0.67398137

00:09:58.932 --> 00:10:02.772 between ligand and glutamate.

NOTE Confidence: 0.67398137

00:10:02.772 --> 00:10:04.278 However,

NOTE Confidence: 0.67398137

00:10:04.280 --> 00:10:07.760 when he administered an agonist,

NOTE Confidence: 0.67398137

00:10:07.760 --> 00:10:08.432 however, sorry,

NOTE Confidence: 0.67398137

00:10:08.432 --> 00:10:10.448 he was trying to also measure

NOTE Confidence: 0.67398137

00:10:10.448 --> 00:10:11.120 internalized receptors.

NOTE Confidence: 0.67398137

00:10:11.120 --> 00:10:14.312 And he could not measure internalized

NOTE Confidence: 0.67398137

00:10:14.312 --> 00:10:15.908 receptors without administering

NOTE Confidence: 0.67398137

00:10:15.908 --> 00:10:18.310 something that's going to permealize the

NOTE Confidence: 0.67398137

00:10:18.310 --> 00:10:21.075 membrane and let the radio ligand in.

NOTE Confidence: 0.67398137

00:10:21.080 --> 00:10:24.257 So here we see that the radio ligand cannot

NOTE Confidence: 0.67398137

00:10:24.257 --> 00:10:27.356 cross the membrane and bind to Homer cells.

NOTE Confidence: 0.67398137

00:10:27.360 --> 00:10:29.958 But when they permealize the membrane,

NOTE Confidence: 0.67398137

00:10:29.960 --> 00:10:33.166 the radio ligand can bind and

NOTE Confidence: 0.67398137

00:10:33.166 --> 00:10:34.264 same thing here.

NOTE Confidence: 0.67398137

00:10:34.264 --> 00:10:36.964 And blue is the typical binding,

NOTE Confidence: 0.67398137

00:10:36.964 --> 00:10:39.487 in red is just sending the

NOTE Confidence: 0.67398137

00:10:39.487 --> 00:10:41.581 radioligand in it cannot cross the

NOTE Confidence: 0.67398137

00:10:41.581 --> 00:10:43.957 and bind to internalized receptors.

NOTE Confidence: 0.67398137

00:10:43.960 --> 00:10:46.256 And in purple when we make little holes

NOTE Confidence: 0.67398137

00:10:46.256 --> 00:10:48.637 in the membrane with the detergent,

NOTE Confidence: 0.67398137

00:10:48.640 --> 00:10:50.728 it can cross the membrane and

NOTE Confidence: 0.67398137

00:10:50.728 --> 00:10:52.120 bind to internalized receptors.

NOTE Confidence: 0.67398137

00:10:52.120 --> 00:10:54.766 So this is really second really

NOTE Confidence: 0.67398137

00:10:54.766 --> 00:10:57.153 important concept that our radioligands

NOTE Confidence: 0.67398137

00:10:57.153 --> 00:10:59.341 cannot bind to internalized

NOTE Confidence: 0.67398137

00:10:59.341 --> 00:11:02.076 receptors unless they get help.

NOTE Confidence: 0.67398137

00:11:02.080 --> 00:11:04.096 And so I was really excited to see that

NOTE Confidence: 0.67398137

00:11:04.096 --> 00:11:06.036 because it really explains some of my work.

NOTE Confidence: 0.67398137

00:11:06.040 --> 00:11:06.415 However,

NOTE Confidence: 0.67398137

00:11:06.415 --> 00:11:08.665 when I presented my data conferences

NOTE Confidence: 0.67398137

00:11:08.665 --> 00:11:10.998 or was trying to publish papers,

NOTE Confidence: 0.67398137

00:11:11.000 --> 00:11:11.848 people said,

NOTE Confidence: 0.67398137

00:11:11.848 --> 00:11:12.272 well,

NOTE Confidence: 0.67398137

00:11:12.272 --> 00:11:14.392 how come your radioligand passes

NOTE Confidence: 0.67398137

00:11:14.392 --> 00:11:16.844 through the the vein barrier but

NOTE Confidence: 0.67398137

00:11:16.844 --> 00:11:18.540 cannot pass through the membrane.

NOTE Confidence: 0.67398137

00:11:18.540 --> 00:11:21.400 So I went back to Jonathan and he showed you.

NOTE Confidence: 0.67398137

00:11:21.400 --> 00:11:23.596 So this is what I just showed you before.

NOTE Confidence: 0.67398137

00:11:23.600 --> 00:11:28.478 He showed that the radioligand these

NOTE Confidence: 0.67398137

00:11:28.480 --> 00:11:30.904 MGO 5 ligands actually cannot on

NOTE Confidence: 0.67398137

00:11:30.904 --> 00:11:33.466 their own pass the DVB that they

NOTE Confidence: 0.67398137

00:11:33.466 --> 00:11:35.344 need a transporter to get them

NOTE Confidence: 0.67398137

00:11:35.344 --> 00:11:37.238 through the blood brain barrier.

NOTE Confidence: 0.67398137

00:11:37.240 --> 00:11:39.022 So this is again really important

NOTE Confidence: 0.67398137

00:11:39.022 --> 00:11:41.048 because a lot of the other

NOTE Confidence: 0.67398137

00:11:41.048 --> 00:11:43.364 ligands that we study can actually

NOTE Confidence: 0.67398137

00:11:43.364 --> 00:11:44.800 measure internalized receptors.

NOTE Confidence: 0.67398137

00:11:44.800 --> 00:11:46.774 And so the explanation of what

NOTE Confidence: 0.67398137

00:11:46.774 --> 00:11:48.090 it is that we're

NOTE Confidence: 0.55249465

00:11:48.160 --> 00:11:50.398 seeing is going to be different.

NOTE Confidence: 0.55249465

00:11:50.400 --> 00:11:52.638 And then the third caveat of

NOTE Confidence: 0.55249465

00:11:52.638 --> 00:11:54.668 studying Mglo Five came initially

NOTE Confidence: 0.55249465

00:11:54.668 --> 00:11:57.434 from studies by Chrissy de Lorenzo,

NOTE Confidence: 0.55249465

00:11:57.440 --> 00:11:59.645 who was at Columbia when she did

NOTE Confidence: 0.55249465

00:11:59.645 --> 00:12:01.864 this first study and then she did

NOTE Confidence: 0.55249465

00:12:01.864 --> 00:12:03.676 the second study here at Yale.

NOTE Confidence: 0.55249465

00:12:03.680 --> 00:12:06.680 So when we bring up new radio ligands,

NOTE Confidence: 0.55249465

00:12:06.680 --> 00:12:08.985 we go through different processes

NOTE Confidence: 0.55249465

00:12:08.985 --> 00:12:11.807 of studying them in cells and

NOTE Confidence: 0.55249465

00:12:11.807 --> 00:12:13.957 animal models and then human.

NOTE Confidence: 0.55249465

00:12:13.960 --> 00:12:15.920 And to study in human,

NOTE Confidence: 0.55249465

00:12:15.920 --> 00:12:17.536 we need to do test, retest studies.

NOTE Confidence: 0.55249465

00:12:17.536 --> 00:12:20.320 So we administer the ligand in the morning,

NOTE Confidence: 0.55249465

00:12:20.320 --> 00:12:22.448 then we give the subjects a break

NOTE Confidence: 0.55249465

00:12:22.448 --> 00:12:24.012 and minister in the afternoon

NOTE Confidence: 0.55249465

00:12:24.012 --> 00:12:26.348 and we want to make sure that the

NOTE Confidence: 0.55249465

00:12:26.411 --> 00:12:28.399 test retest is within 10 to 15%.

NOTE Confidence: 0.55249465

00:12:28.400 --> 00:12:31.074 So that every time that you measure,

NOTE Confidence: 0.55249465

00:12:31.080 --> 00:12:32.480 whatever it is you're trying to measure,

NOTE Confidence: 0.55249465

00:12:32.480 --> 00:12:34.600 it is the same thing that you're measuring,

NOTE Confidence: 0.55249465

00:12:34.600 --> 00:12:37.558 that there are no significant differences.

NOTE Confidence: 0.55249465

00:12:37.560 --> 00:12:38.760 And so back in the day,

NOTE Confidence: 0.55249465

00:12:38.760 --> 00:12:40.385 these studies were done only

NOTE Confidence: 0.55249465

00:12:40.385 --> 00:12:41.360 in male subjects.

NOTE Confidence: 0.55249465

00:12:41.360 --> 00:12:44.000 So Chrissy had nine subjects participate.

NOTE Confidence: 0.55249465

00:12:44.000 --> 00:12:47.318 They were all new to PET scanning

NOTE Confidence: 0.55249465

00:12:47.320 --> 00:12:51.192 and contrary to the 1015 plus minus

NOTE Confidence: 0.55249465

00:12:51.192 --> 00:12:53.600 test 3 test that we typically see,

NOTE Confidence: 0.55249465

00:12:53.600 --> 00:12:57.048 Chrissy showed about 20 to 40% plus.

NOTE Confidence: 0.55249465

00:12:57.048 --> 00:12:59.320 So in the morning,

NOTE Confidence: 0.55249465

00:12:59.320 --> 00:13:01.870 subjects were scanned and then their

NOTE Confidence: 0.55249465

00:13:01.870 --> 00:13:03.570 receptor availabilities appeared to

NOTE Confidence: 0.55249465

00:13:03.633 --> 00:13:05.757 go up in the afternoon by 20 to 40%.

NOTE Confidence: 0.55249465

00:13:05.760 --> 00:13:08.118 And so this was really puzzling.

NOTE Confidence: 0.55249465

00:13:08.120 --> 00:13:09.436 And we were trying to figure out,

NOTE Confidence: 0.55249465

00:13:09.440 --> 00:13:11.148 is it because people were anxious because

NOTE Confidence: 0.55249465

00:13:11.148 --> 00:13:12.717 I've never had a PET scan before,

NOTE Confidence: 0.55249465

00:13:12.720 --> 00:13:14.351 so they're anxious in the morning and

NOTE Confidence: 0.55249465

00:13:14.351 --> 00:13:16.676 then in the afternoon they're not so anxious.

NOTE Confidence: 0.55249465

00:13:16.680 --> 00:13:18.320 Or was there something else?

NOTE Confidence: 0.55249465

00:13:18.320 --> 00:13:20.120 Was there heart rate, you know,

NOTE Confidence: 0.55249465

00:13:20.120 --> 00:13:21.476 or blood pressure higher in the

NOTE Confidence: 0.55249465

00:13:21.476 --> 00:13:23.400 morning or like, what was going on?

NOTE Confidence: 0.55249465

00:13:23.400 --> 00:13:24.640 And in the meantime,

NOTE Confidence: 0.55249465

00:13:24.640 --> 00:13:26.660 we all thought this was AVP 688.

NOTE Confidence: 0.55249465

00:13:26.660 --> 00:13:28.040 We all thought that this was a bad lag.

NOTE Confidence: 0.55249465

00:13:28.040 --> 00:13:30.147 And so I was doing test retest

NOTE Confidence: 0.55249465

00:13:30.147 --> 00:13:32.398 studies on the same day with FBAB.

NOTE Confidence: 0.55249465

00:13:32.400 --> 00:13:33.740 But Chrissy was persistent,

NOTE Confidence: 0.55249465

00:13:33.740 --> 00:13:35.080 and she did test,

NOTE Confidence: 0.55249465

00:13:35.080 --> 00:13:36.102 retest again,

NOTE Confidence: 0.55249465

00:13:36.102 --> 00:13:39.168 this time at Yale with female

NOTE Confidence: 0.55249465

00:13:39.168 --> 00:13:40.720 participants as well.

NOTE Confidence: 0.55249465

00:13:40.720 --> 00:13:43.801 And so this is AVP 688 showing

NOTE Confidence: 0.55249465

00:13:43.801 --> 00:13:46.206 increases in the afternoon scan

NOTE Confidence: 0.55249465

00:13:46.206 --> 00:13:49.519 binding in male and female subjects.

NOTE Confidence: 0.55249465

00:13:49.520 --> 00:13:52.275 And then this is FBEB showing

NOTE Confidence: 0.55249465

00:13:52.275 --> 00:13:54.250 increases in the afternoon scan

NOTE Confidence: 0.55249465

00:13:54.250 --> 00:13:56.520 in female and male subjects.

NOTE Confidence: 0.55249465

00:13:56.520 --> 00:13:59.080 And if you see here,

NOTE Confidence: 0.55249465

00:13:59.080 --> 00:14:00.900 so the females are in red and

NOTE Confidence: 0.55249465

00:14:00.900 --> 00:14:02.320 the males are in blue.

NOTE Confidence: 0.55249465

00:14:02.320 --> 00:14:05.820 Females showed a greater increase in the

NOTE Confidence: 0.55249465

00:14:05.820 --> 00:14:08.959 afternoon scan as compared to males.

NOTE Confidence: 0.55249465

00:14:08.960 --> 00:14:10.436 And so we started you know,

NOTE Confidence: 0.55249465

00:14:10.440 --> 00:14:11.172 reading literature.

NOTE Confidence: 0.55249465

00:14:11.172 --> 00:14:13.368 We also took people's heart rates

NOTE Confidence: 0.55249465

00:14:13.368 --> 00:14:15.310 and blood pressure and their

NOTE Confidence: 0.55249465

00:14:15.310 --> 00:14:16.826 anxiety levels etcetera, etcetera.

NOTE Confidence: 0.55249465

00:14:16.826 --> 00:14:19.437 But nothing could really well explain this,

NOTE Confidence: 0.55249465

00:14:19.440 --> 00:14:22.950 you know 20 to like 80% increase in

NOTE Confidence: 0.55249465

00:14:22.950 --> 00:14:25.560 receptor availability over a few hours.

NOTE Confidence: 0.55249465

00:14:25.560 --> 00:14:27.876 And we read some animal work,

NOTE Confidence: 0.55249465

00:14:27.880 --> 00:14:29.384 some medication development work.

NOTE Confidence: 0.55249465

00:14:29.384 --> 00:14:32.050 And what became apparent to us was

NOTE Confidence: 0.55249465

00:14:32.050 --> 00:14:34.114 that we weren't studying test retest.

NOTE Confidence: 0.55249465

00:14:34.120 --> 00:14:36.598 We were studying during our variation.

NOTE Confidence: 0.55249465

00:14:36.600 --> 00:14:38.736 So for those of you who are not

NOTE Confidence: 0.55249465

00:14:38.736 --> 00:14:40.520 familiar with the cortisol system,

NOTE Confidence: 0.55249465

00:14:40.520 --> 00:14:43.400 cortisol levels in humans increase

NOTE Confidence: 0.55249465

00:14:43.400 --> 00:14:45.178 overnight and in the morning we wake

NOTE Confidence: 0.55249465

00:14:45.178 --> 00:14:47.158 up because of higher cortisol levels.

NOTE Confidence: 0.3123216

00:14:47.160 --> 00:14:48.826 We're more alert. We're ready to go

NOTE Confidence: 0.3123216

00:14:48.826 --> 00:14:50.638 maybe a little chocolate or caffeine,

NOTE Confidence: 0.3123216

00:14:50.640 --> 00:14:52.544 but you know, we're ready to start

NOTE Confidence: 0.3123216

00:14:52.544 --> 00:14:55.040 the day and get to work and do stuff.

NOTE Confidence: 0.3123216

00:14:55.040 --> 00:14:58.510 And then over the afternoon our corisol

NOTE Confidence: 0.3123216

00:14:58.510 --> 00:15:00.995 levels decrease and we get more tired,

NOTE Confidence: 0.3123216

00:15:01.000 --> 00:15:02.328 a bit more lethargic.

NOTE Confidence: 0.3123216

00:15:02.328 --> 00:15:05.112 We're kind of done with the day and by

NOTE Confidence: 0.3123216

00:15:05.112 --> 00:15:06.648 evening they're the lowest and that's

NOTE Confidence: 0.3123216

00:15:06.648 --> 00:15:08.439 when we are ready to go to sleep.

NOTE Confidence: 0.3123216

00:15:08.440 --> 00:15:10.240 And then the cycle continues.

NOTE Confidence: 0.3123216

00:15:10.240 --> 00:15:12.440 Well, animal literature shows that

NOTE Confidence: 0.3123216

00:15:12.440 --> 00:15:14.222 administration of cortisone actually

NOTE Confidence: 0.3123216

00:15:14.222 --> 00:15:17.456 decreases Anglo 5 S increases in Corso

NOTE Confidence: 0.3123216

00:15:17.456 --> 00:15:20.000 levels decrease Anglo 5 availability.

NOTE Confidence: 0.3123216

00:15:20.000 --> 00:15:22.846 So what we think is happening in our

NOTE Confidence: 0.3123216

00:15:22.846 --> 00:15:25.247 test retest scanning is that in the

NOTE Confidence: 0.3123216

00:15:25.247 --> 00:15:27.716 morning when Corso levels are highest,

NOTE Confidence: 0.3123216

00:15:27.720 --> 00:15:30.318 we're observing lower Anglo 5 availability.

NOTE Confidence: 0.3123216

00:15:30.320 --> 00:15:32.952 In the afternoon when the Corso levels

NOTE Confidence: 0.3123216

00:15:32.952 --> 00:15:35.895 are much lower for observing greater

NOTE Confidence: 0.3123216

00:15:35.895 --> 00:15:38.315 or higher amplified availability.

NOTE Confidence: 0.3123216

00:15:38.320 --> 00:15:40.742 So in so the test retest studies

NOTE Confidence: 0.3123216

00:15:40.742 --> 00:15:43.832 were really are not accurate but are

NOTE Confidence: 0.3123216

00:15:43.832 --> 00:15:45.680 measuring journal variation which

NOTE Confidence: 0.3123216

00:15:45.680 --> 00:15:47.120 actually was something interesting.

NOTE Confidence: 0.3123216

00:15:47.120 --> 00:15:48.080 And based on these data,

NOTE Confidence: 0.3123216

00:15:48.080 --> 00:15:51.328 Chrissy got an RO one to study circadian

NOTE Confidence: 0.3123216

00:15:51.328 --> 00:15:54.253 rhythm and sleep wake cycle in people

NOTE Confidence: 0.3123216

00:15:54.253 --> 00:15:57.639 who are controls and who have depression.

NOTE Confidence: 0.3123216

00:15:57.640 --> 00:15:59.978 And so these were the many caveats

NOTE Confidence: 0.3123216

00:15:59.978 --> 00:16:01.520 of studying amplified in Viva.

NOTE Confidence: 0.41547155

00:16:04.040 --> 00:16:08.036 And now I'll show you our work in psychiatry.

NOTE Confidence: 0.41547155

00:16:08.040 --> 00:16:11.619 So this was maybe in 2008 or 2010

NOTE Confidence: 0.41547155

00:16:11.619 --> 00:16:14.370 long time ago that we decided to

NOTE Confidence: 0.41547155

00:16:14.463 --> 00:16:16.677 study Anglu 5 in unipolar depression.

NOTE Confidence: 0.41547155

00:16:16.677 --> 00:16:19.692 And I showed you that Anglu 5 is

NOTE Confidence: 0.41547155

00:16:19.692 --> 00:16:21.837 important to our daily functioning.

NOTE Confidence: 0.41547155

00:16:21.840 --> 00:16:24.288 And at that time, a lot of pharma

NOTE Confidence: 0.41547155

00:16:24.288 --> 00:16:26.689 studies were studying Anglu 5 agent

NOTE Confidence: 0.41547155

00:16:26.689 --> 00:16:28.834 agents for treatment of depression.

NOTE Confidence: 0.41547155

00:16:28.840 --> 00:16:30.954 But there was no work in human,

NOTE Confidence: 0.41547155

00:16:30.960 --> 00:16:33.640 a lot of the work was done in animal studies.

NOTE Confidence: 0.41547155

00:16:33.640 --> 00:16:36.484 And so we thought that it would be good

NOTE Confidence: 0.41547155

00:16:36.484 --> 00:16:39.304 to to invivo human work and see if Mglu

NOTE Confidence: 0.41547155

00:16:39.304 --> 00:16:41.344 5 actually plays a role in depression.

NOTE Confidence: 0.41547155

00:16:41.344 --> 00:16:44.199 At the same time as I was writing that grant,

NOTE Confidence: 0.41547155

00:16:44.200 --> 00:16:46.240 this was a Dana grant.

NOTE Confidence: 0.41547155

00:16:46.240 --> 00:16:48.400 There was a preliminary study published

NOTE Confidence: 0.41547155

00:16:48.400 --> 00:16:50.574 by Gregor Hessler's group showing in

NOTE Confidence: 0.41547155

00:16:50.574 --> 00:16:52.776 11 people with depression and then

NOTE Confidence: 0.41547155

00:16:52.776 --> 00:16:55.660 they also had postmortem group that

NOTE Confidence: 0.41547155

00:16:55.660 --> 00:17:00.454 MGLU 5 availability is lower and lower

NOTE Confidence: 0.41547155

00:17:00.454 --> 00:17:03.189 angulified availability was in their

NOTE Confidence: 0.41547155

00:17:03.189 --> 00:17:06.280 group associated with anxiety symptoms.

NOTE Confidence: 0.41547155

00:17:06.280 --> 00:17:08.653 And so I had the opportunity to

NOTE Confidence: 0.41547155

00:17:08.653 --> 00:17:11.520 study a much larger group of people.

NOTE Confidence: 0.41547155

00:17:11.520 --> 00:17:15.240 And so we scanned 30 subjects with MDD,

NOTE Confidence: 0.41547155

00:17:15.240 --> 00:17:18.240 which for PET is quite a large study.

NOTE Confidence: 0.41547155

00:17:18.240 --> 00:17:20.640 They were all unmedicated 35 years

NOTE Confidence: 0.41547155

00:17:20.640 --> 00:17:22.240 of age on average.

NOTE Confidence: 0.41547155

00:17:22.240 --> 00:17:23.976 Average depression scores we

NOTE Confidence: 0.41547155

00:17:23.976 --> 00:17:25.278 measured with PDI,

NOTE Confidence: 0.41547155

00:17:25.280 --> 00:17:28.520 modulus and AMD and then we had 35

NOTE Confidence: 0.41547155

00:17:28.520 --> 00:17:31.318 healthy controls who were matched by sex,

NOTE Confidence: 0.41547155

00:17:31.320 --> 00:17:33.420 age and smoking status.

NOTE Confidence: 0.41547155

00:17:33.420 --> 00:17:36.650 None of them had significant personal

NOTE Confidence: 0.41547155

00:17:36.650 --> 00:17:39.475 psychiatric history or first degree

NOTE Confidence: 0.41547155

00:17:39.475 --> 00:17:41.800 relative with psychiatric history,

NOTE Confidence: 0.41547155

00:17:41.800 --> 00:17:44.280 and subjects did PET scan, Mrs.

NOTE Confidence: 0.41547155

00:17:44.280 --> 00:17:45.560 and MRI,

NOTE Confidence: 0.41547155

00:17:45.560 --> 00:17:46.840 and Mrs.

NOTE Confidence: 0.41547155

00:17:46.840 --> 00:17:49.120 stands for magnetic resonance spectroscopy.

NOTE Confidence: 0.41547155

00:17:49.120 --> 00:17:51.848 This part of the study was done in

NOTE Confidence: 0.41547155

00:17:51.848 --> 00:17:53.440 collaboration with Graham Mason.

NOTE Confidence: 0.41547155

00:17:53.440 --> 00:17:55.743 We use a magnet to study metabolic

NOTE Confidence: 0.41547155

00:17:55.743 --> 00:17:57.200 changes in the brain.

NOTE Confidence: 0.41547155

00:17:57.200 --> 00:17:59.006 All the measurements are in tissue

NOTE Confidence: 0.41547155

00:17:59.006 --> 00:18:01.040 and when when we get the data,

NOTE Confidence: 0.41547155

00:18:01.040 --> 00:18:03.384 it's put into a spectrum and each metabolite

NOTE Confidence: 0.41547155

00:18:03.384 --> 00:18:05.440 has its own peak in the spectrum.

NOTE Confidence: 0.41547155

00:18:05.440 --> 00:18:07.841 And so this was back back in

NOTE Confidence: 0.41547155

00:18:07.841 --> 00:18:10.489 the day when we couldn't really

NOTE Confidence: 0.41547155

00:18:10.489 --> 00:18:13.555 separate glutamate and GLN too well.

NOTE Confidence: 0.41547155

00:18:13.560 --> 00:18:14.644 So we studied GLX,

NOTE Confidence: 0.41547155

00:18:14.644 --> 00:18:17.119 which is the sum of glutamate and glutamine.

NOTE Confidence: 0.8321714

00:18:19.520 --> 00:18:22.700 And the other caveat with Mrs. is that,

NOTE Confidence: 0.8321714

00:18:22.700 --> 00:18:25.280 especially when I started doing this,

NOTE Confidence: 0.8321714

00:18:25.280 --> 00:18:27.760 we could only do one voxel at a time because

NOTE Confidence: 0.8321714

00:18:27.821 --> 00:18:30.071 it took us about two hours to do 1 scan.

NOTE Confidence: 0.8321714

00:18:30.080 --> 00:18:31.694 And as you can imagine, the subjects

NOTE Confidence: 0.8321714

00:18:31.694 --> 00:18:33.510 were not going to be in the scanner

NOTE Confidence: 0.8321714

00:18:33.560 --> 00:18:35.360 for four hours for us to get 2 voxels.

NOTE Confidence: 0.8321714

00:18:35.360 --> 00:18:37.705 And so we decided to study the

NOTE Confidence: 0.8321714

00:18:37.705 --> 00:18:39.313 anterior singular cortex given its

NOTE Confidence: 0.8321714

00:18:39.313 --> 00:18:43.438 role in mood and cognitive processes.

NOTE Confidence: 0.8321714

00:18:43.440 --> 00:18:45.960 And so this is our main outcome.

NOTE Confidence: 0.8321714

00:18:45.960 --> 00:18:48.193 So the healthy controls are in diamonds

NOTE Confidence: 0.8321714

00:18:48.193 --> 00:18:50.510 and people with depression are in circles.

NOTE Confidence: 0.8321714

00:18:50.510 --> 00:18:52.990 We did not see any differences between groups

NOTE Confidence: 0.8321714

00:18:52.990 --> 00:18:55.319 in any of the regions that we assessed.

NOTE Confidence: 0.8321714

00:18:55.320 --> 00:18:57.528 And with that you can look across

NOTE Confidence: 0.8321714

00:18:57.528 --> 00:19:00.104 the whole brain and we saw nothing

NOTE Confidence: 0.8321714

00:19:00.104 --> 00:19:01.759 across the whole brain.

NOTE Confidence: 0.8321714

00:19:01.760 --> 00:19:05.600 The previous study used a reference

NOTE Confidence: 0.8321714

00:19:05.600 --> 00:19:07.700 region to calculate their outcomes.

NOTE Confidence: 0.8321714

00:19:07.700 --> 00:19:09.525 So even though Anglo fives

NOTE Confidence: 0.8321714

00:19:09.525 --> 00:19:11.438 are everywhere in the brain,

NOTE Confidence: 0.8321714

00:19:11.440 --> 00:19:14.038 I decided to try that too,

NOTE Confidence: 0.8321714

00:19:14.040 --> 00:19:16.420 because maybe that was the difference of

NOTE Confidence: 0.8321714

00:19:16.420 --> 00:19:18.870 why would it not see significant findings.

NOTE Confidence: 0.8321714

00:19:18.870 --> 00:19:21.600 And again, whether we use blood

NOTE Confidence: 0.8321714

00:19:21.600 --> 00:19:23.598 or cerebellum as a reference,

NOTE Confidence: 0.8321714

00:19:23.600 --> 00:19:26.477 we did not see difference between groups.

NOTE Confidence: 0.8321714

00:19:26.480 --> 00:19:26.716 However,

NOTE Confidence: 0.8321714

00:19:26.716 --> 00:19:28.840 if you go back and look at the literature,

NOTE Confidence: 0.8321714

00:19:28.840 --> 00:19:31.120 we're actually not an odd duck.

NOTE Confidence: 0.8321714

00:19:31.120 --> 00:19:33.010 So there's a postmortem study

NOTE Confidence: 0.8321714

00:19:33.010 --> 00:19:34.522 showing no differences between

NOTE Confidence: 0.8321714

00:19:34.522 --> 00:19:36.439 controls and people with depression,

NOTE Confidence: 0.8321714

00:19:36.440 --> 00:19:38.800 with psychosis or no psychosis,

NOTE Confidence: 0.8321714

00:19:38.800 --> 00:19:40.105 and amplified availability.

NOTE Confidence: 0.8321714

00:19:40.105 --> 00:19:43.191 And then we did our own autobadiography

NOTE Confidence: 0.8321714

00:19:43.191 --> 00:19:46.017 study was showing no differences between

NOTE Confidence: 0.8321714

00:19:46.017 --> 00:19:48.211 people with depression as compared

NOTE Confidence: 0.8321714

00:19:48.211 --> 00:19:50.359 to controls in Anglo 5 availability,

NOTE Confidence: 0.8321714

00:19:50.360 --> 00:19:52.640 although there's a little more

NOTE Confidence: 0.8321714

00:19:52.640 --> 00:19:54.920 variability in the MDT group.

NOTE Confidence: 0.8321714

00:19:54.920 --> 00:19:58.720 The novel part is that we of course did Mrs.

NOTE Confidence: 0.8321714

00:19:58.720 --> 00:20:03.680 with PET and so we saw higher glutamate,

NOTE Confidence: 0.8321714

00:20:03.680 --> 00:20:05.870 glutamine and GLX levels in people

NOTE Confidence: 0.8321714

00:20:05.870 --> 00:20:07.716 with depression as compared to

NOTE Confidence: 0.8321714

00:20:07.716 --> 00:20:10.080 controls and when we looked at

NOTE Confidence: 0.8321714

00:20:10.080 --> 00:20:12.411 relationship between glutamate.

NOTE Confidence: 0.8321714

00:20:12.411 --> 00:20:17.073 Or G glutamine or GLX and

NOTE Confidence: 0.8321714

00:20:17.080 --> 00:20:17.944 receptor availability,

NOTE Confidence: 0.8321714

00:20:17.944 --> 00:20:20.536 we saw that people who had

NOTE Confidence: 0.8321714

00:20:20.536 --> 00:20:21.920 greater glutamate levels,

NOTE Confidence: 0.8321714

00:20:21.920 --> 00:20:24.758 et cetera had low receptor availability.

NOTE Confidence: 0.8321714

00:20:24.760 --> 00:20:26.956 So this really makes sense that

NOTE Confidence: 0.8321714

00:20:26.960 --> 00:20:29.438 higher endogenous neurotransmitter

NOTE Confidence: 0.8321714

00:20:29.438 --> 00:20:32.914 would down regulate receptors which

NOTE Confidence: 0.8321714

00:20:32.914 --> 00:20:35.399 would then in turn internalize.

NOTE Confidence: 0.8321714

00:20:35.400 --> 00:20:36.966 But this has never been shown

NOTE Confidence: 0.8321714

00:20:36.966 --> 00:20:38.360 in human in the vivo.

NOTE Confidence: 0.8321714

00:20:38.360 --> 00:20:41.360 We've hypothesized for years that

NOTE Confidence: 0.8321714

00:20:41.360 --> 00:20:42.800 too much glutamate is excited,

NOTE Confidence: 0.8321714

00:20:42.800 --> 00:20:43.036 toxic,

NOTE Confidence: 0.8321714

00:20:43.036 --> 00:20:44.452 but that's the first time we

NOTE Confidence: 0.8321714

00:20:44.452 --> 00:20:46.000 were able to show it in vivo,

NOTE Confidence: 0.8321714

00:20:46.000 --> 00:20:48.560 and this was really exciting.

NOTE Confidence: 0.8321714

00:20:48.560 --> 00:20:54.370 So this work has been published and

NOTE Confidence: 0.8321714

00:20:54.370 --> 00:20:57.172 has given the rise to a lot of other

NOTE Confidence: 0.8321714

00:20:57.172 --> 00:20:58.797 work that I won't now show you,

NOTE Confidence: 0.8321714

00:20:58.800 --> 00:21:00.998 some of which has now been published.

NOTE Confidence: 0.8321714

00:21:01.000 --> 00:21:04.164 So my first R1 was actually looking

NOTE Confidence: 0.8321714

00:21:04.164 --> 00:21:08.304 at Anglo 5 as a marker to help us

NOTE Confidence: 0.8321714

00:21:08.304 --> 00:21:10.160 differentiate depression during bipolar

NOTE Confidence: 0.8321714

00:21:10.241 --> 00:21:12.596 disorder versus in unipolar disorder.

NOTE Confidence: 0.8321714

00:21:12.596 --> 00:21:15.230 And this work was done in

NOTE Confidence: 0.8321714

00:21:15.313 --> 00:21:18.157 collaboration with Hilary Blumberg.

NOTE Confidence: 0.8321714

00:21:18.160 --> 00:21:20.720 And so we recruited people who are controls,

NOTE Confidence: 0.8321714

00:21:20.720 --> 00:21:22.960 people who have bipolar depression,

NOTE Confidence: 0.8321714

00:21:22.960 --> 00:21:25.160 people who have bipolar euthymia,

NOTE Confidence: 0.8321714

00:21:25.160 --> 00:21:27.757 and then people who have unipolar depression.

NOTE Confidence: 0.8321714

00:21:27.760 --> 00:21:30.120 And although the grant did

NOTE Confidence: 0.8321714

00:21:30.120 --> 00:21:32.480 not call for bipolar Euthymia,

NOTE Confidence: 0.8321714

00:21:32.480 --> 00:21:34.400 but when we recruited people and

NOTE Confidence: 0.8321714

00:21:34.400 --> 00:21:36.297 we did their screening and then

NOTE Confidence: 0.8321714

00:21:36.297 --> 00:21:37.953 they showed up for PET scans,

NOTE Confidence: 0.28242582

00:21:37.960 --> 00:21:39.880 they were in whatever mood episode,

NOTE Confidence: 0.28242582

00:21:39.880 --> 00:21:42.424 you know, because people depression cycle

NOTE Confidence: 0.28242582

00:21:42.424 --> 00:21:45.179 with bipolar disorder cycle quite a bit.

NOTE Confidence: 0.28242582

00:21:45.179 --> 00:21:48.146 So we amended our protocol and let people

NOTE Confidence: 0.28242582

00:21:48.146 --> 00:21:52.758 with any mood state participate in the study.

NOTE Confidence: 0.28242582

00:21:52.760 --> 00:21:54.160 So there are no differences

NOTE Confidence: 0.28242582

00:21:54.160 --> 00:21:55.280 between subjects and age,

NOTE Confidence: 0.28242582

00:21:55.280 --> 00:21:57.800 sex, smoking status, etcetera,

NOTE Confidence: 0.28242582

00:21:57.800 --> 00:22:00.320 except for depression status.

NOTE Confidence: 0.28242582

00:22:00.320 --> 00:22:02.324 So people with bipolar disorder who

NOTE Confidence: 0.28242582

00:22:02.324 --> 00:22:04.068 are depressed and unipolar disorder

NOTE Confidence: 0.28242582

00:22:04.068 --> 00:22:05.870 who are depressed or more significantly

NOTE Confidence: 0.28242582

00:22:05.870 --> 00:22:07.120 depressed than any other group,

NOTE Confidence: 0.28242582

00:22:07.120 --> 00:22:10.840 another group was depressed.

NOTE Confidence: 0.28242582

00:22:10.840 --> 00:22:13.108 And so these are our data that

NOTE Confidence: 0.28242582

00:22:13.108 --> 00:22:14.936 were recently published with Sophie

NOTE Confidence: 0.28242582

00:22:14.936 --> 00:22:17.076 Holmes and Booth Ashe leading

NOTE Confidence: 0.28242582

00:22:17.080 --> 00:22:18.960 the writing of the manuscript.

NOTE Confidence: 0.28242582

00:22:18.960 --> 00:22:21.473 And so we see that people who

NOTE Confidence: 0.28242582

00:22:21.473 --> 00:22:23.000 are controls aren't grey,

NOTE Confidence: 0.28242582

00:22:23.000 --> 00:22:24.680 people with unipolar depression

NOTE Confidence: 0.28242582

00:22:24.680 --> 00:22:25.520 aren't orange.

NOTE Confidence: 0.28242582

00:22:25.520 --> 00:22:25.912 Again,

NOTE Confidence: 0.28242582

00:22:25.912 --> 00:22:27.480 there's no difference receptor

NOTE Confidence: 0.28242582

00:22:27.480 --> 00:22:29.048 availability between these two

NOTE Confidence: 0.28242582

00:22:29.048 --> 00:22:31.360 groups as we showed previously.

NOTE Confidence: 0.28242582

00:22:31.360 --> 00:22:33.760 And then people bipolar disorder

NOTE Confidence: 0.28242582

00:22:33.760 --> 00:22:36.371 who are depressed or in purple and

NOTE Confidence: 0.28242582

00:22:36.371 --> 00:22:39.557 who are euthymic are in turquoise

NOTE Confidence: 0.28242582

00:22:39.560 --> 00:22:41.639 and both of these groups are lower

NOTE Confidence: 0.28242582

00:22:41.639 --> 00:22:42.973 in their receptor availability

NOTE Confidence: 0.28242582

00:22:42.973 --> 00:22:45.666 as compared to controls and are

NOTE Confidence: 0.28242582

00:22:45.666 --> 00:22:47.238 unipolar depressed.

NOTE Confidence: 0.28242582

00:22:47.240 --> 00:22:49.118 And this was across brain regions.

NOTE Confidence: 0.28242582

00:22:49.120 --> 00:22:50.720 The prefrontal cortical regions

NOTE Confidence: 0.28242582

00:22:50.720 --> 00:22:52.445 were my main hypothesis,

NOTE Confidence: 0.28242582

00:22:52.445 --> 00:22:56.220 but this was across the brain and

NOTE Confidence: 0.28242582

00:22:56.220 --> 00:22:59.940 what was really interesting as well

NOTE Confidence: 0.28242582

00:22:59.940 --> 00:23:02.756 is not only is Amglo 5 availability

NOTE Confidence: 0.28242582

00:23:02.756 --> 00:23:04.220 different between people bipolar

NOTE Confidence: 0.28242582

00:23:04.282 --> 00:23:06.198 disorder versus unipolar disorder,

NOTE Confidence: 0.28242582

00:23:06.200 --> 00:23:09.853 but its relationship to mood and

NOTE Confidence: 0.28242582

00:23:09.853 --> 00:23:13.718 cognitive functioning was also different.

NOTE Confidence: 0.28242582

00:23:13.720 --> 00:23:16.717 So this shows us that Amglo 5 can help

NOTE Confidence: 0.28242582

00:23:16.717 --> 00:23:19.120 potentially to differentiate to disorders,

NOTE Confidence: 0.28242582

00:23:19.120 --> 00:23:22.288 but may also be treatment targets

NOTE Confidence: 0.28242582

00:23:22.288 --> 00:23:24.400 specifically for bipolar disorder.

NOTE Confidence: 0.28242582

00:23:24.400 --> 00:23:29.687 And we also collected BOLD fMRI and

NOTE Confidence: 0.28242582

00:23:29.687 --> 00:23:32.501 during an emotional processing task that

NOTE Confidence: 0.28242582

00:23:32.501 --> 00:23:35.238 Hillary has extensively published on.

NOTE Confidence: 0.28242582

00:23:35.240 --> 00:23:36.240 And so in this task,

NOTE Confidence: 0.28242582

00:23:36.240 --> 00:23:40.280 people are oriented to happy,

NOTE Confidence: 0.28242582

00:23:40.280 --> 00:23:42.320 neutral or fearful faces.

NOTE Confidence: 0.28242582

00:23:42.320 --> 00:23:45.120 And our data are currently under review.

NOTE Confidence: 0.28242582

00:23:45.120 --> 00:23:47.020 Biological Psychiatry with Ruth

NOTE Confidence: 0.28242582

00:23:47.020 --> 00:23:49.395 Ash being the lead author.

NOTE Confidence: 0.28242582

00:23:49.400 --> 00:23:52.433 And we have people who are controls in black,

NOTE Confidence: 0.28242582

00:23:52.440 --> 00:23:54.252 people with bipolar disorder

NOTE Confidence: 0.28242582

00:23:54.252 --> 00:23:56.517 across smooth states in brown,

NOTE Confidence: 0.28242582

00:23:56.520 --> 00:23:59.243 and then people who are who have

NOTE Confidence: 0.28242582

00:23:59.243 --> 00:24:00.840 unipolar depression in blue.

NOTE Confidence: 0.28242582

00:24:00.840 --> 00:24:03.283 And you can see that the response

NOTE Confidence: 0.28242582

00:24:03.283 --> 00:24:06.464 and the fear task is the same between

NOTE Confidence: 0.28242582

00:24:06.464 --> 00:24:08.514 controls and people with MDD.

NOTE Confidence: 0.28242582

00:24:08.520 --> 00:24:10.920 But people with bipolar disorder

NOTE Confidence: 0.28242582

00:24:10.920 --> 00:24:13.373 have an upregulated response across

NOTE Confidence: 0.28242582

00:24:13.373 --> 00:24:16.038 various clusters in the brain.

NOTE Confidence: 0.28242582

00:24:16.040 --> 00:24:18.728 And when we correlate this response

NOTE Confidence: 0.28242582

00:24:18.728 --> 00:24:20.072 with anglify availability,

NOTE Confidence: 0.28242582

00:24:20.080 --> 00:24:22.300 we also see significant findings

NOTE Confidence: 0.28242582

00:24:22.300 --> 00:24:24.520 in the bipolar group only.

NOTE Confidence: 0.28242582

00:24:24.520 --> 00:24:25.756 So we here,

NOTE Confidence: 0.28242582

00:24:25.756 --> 00:24:28.228 we're seeing that Anglo 5 potentially

NOTE Confidence: 0.28242582

00:24:28.228 --> 00:24:30.477 can help but differentiate BD

NOTE Confidence: 0.28242582

00:24:30.477 --> 00:24:33.560 from MDD across mood,

NOTE Confidence: 0.28242582

00:24:33.560 --> 00:24:37.536 cognitive and bold response measures.

NOTE Confidence: 0.28242582

00:24:37.536 --> 00:24:38.720 And currently,

NOTE Confidence: 0.28242582

00:24:38.720 --> 00:24:42.360 I'm evaluating Anglo 5 to see if it

NOTE Confidence: 0.28242582

00:24:42.360 --> 00:24:45.560 can help us differentiate suicidality

NOTE Confidence: 0.28242582

00:24:45.560 --> 00:24:48.680 in people with bipolar disorder specifically.

NOTE Confidence: 0.28242582

00:24:48.680 --> 00:24:52.135 And this RO one started right before COVID.

NOTE Confidence: 0.28242582

00:24:52.135 --> 00:24:55.412 And so we've not been as successful

NOTE Confidence: 0.28242582

00:24:55.412 --> 00:24:56.716 in these previous studies,

NOTE Confidence: 0.28242582

00:24:56.720 --> 00:24:58.440 but the data collection's ongoing.

NOTE Confidence: 0.28242582

00:24:58.440 --> 00:25:00.176 I'll be happy to present our data

NOTE Confidence: 0.28242582

00:25:00.176 --> 00:25:01.479 in a couple of years,

NOTE Confidence: 0.28242582

00:25:01.480 --> 00:25:04.238 but right now I will switch gears

NOTE Confidence: 0.28242582

00:25:04.238 --> 00:25:05.920 and talk about PTSD.

NOTE Confidence: 0.28242582

00:25:05.920 --> 00:25:07.920 So a few years ago,

NOTE Confidence: 0.28242582

00:25:07.920 --> 00:25:11.914 I was asked to incorporate PTSD and

NOTE Confidence: 0.28242582

00:25:11.914 --> 00:25:15.376 get the PTSD molecular imaging program

NOTE Confidence: 0.28242582

00:25:15.376 --> 00:25:17.910 growing at Yale and in collaboration

NOTE Confidence: 0.28242582

00:25:17.910 --> 00:25:20.280 with the National Center for PTSD.

NOTE Confidence: 0.28242582

00:25:20.280 --> 00:25:23.313 And so I wanted to see if Amglu 5

NOTE Confidence: 0.313723

00:25:23.320 --> 00:25:25.635 availability again can help us

NOTE Confidence: 0.313723

00:25:25.635 --> 00:25:27.950 differentiate people who have PTSD

NOTE Confidence: 0.313723

00:25:28.028 --> 00:25:30.238 versus MDD or bipolar etcetera,

NOTE Confidence: 0.313723

00:25:30.240 --> 00:25:33.600 etcetera in in terms of helping

NOTE Confidence: 0.313723

00:25:33.600 --> 00:25:35.174 them get better treatment.

NOTE Confidence: 0.313723

00:25:35.174 --> 00:25:37.540 And so PTSD is one of the

NOTE Confidence: 0.313723

00:25:37.616 --> 00:25:39.556 newer disorders in the DSM.

NOTE Confidence: 0.313723

00:25:39.560 --> 00:25:42.004 It was established as a diagnosis in 1980,

NOTE Confidence: 0.313723

00:25:42.004 --> 00:25:43.708 and it is the only disorder

NOTE Confidence: 0.313723

00:25:43.708 --> 00:25:45.678 that we know the etiology for.

NOTE Confidence: 0.313723

00:25:45.680 --> 00:25:48.320 There has to have been a traumatic event,

NOTE Confidence: 0.313723

00:25:48.320 --> 00:25:51.162 a criterion, a event that has led

NOTE Confidence: 0.313723

00:25:51.162 --> 00:25:54.319 to this to development of PTSD.

NOTE Confidence: 0.313723

00:25:54.320 --> 00:25:56.672 About 8% of Americans suffer from

NOTE Confidence: 0.313723

00:25:56.672 --> 00:25:59.386 PTSD and this number varies between

NOTE Confidence: 0.313723

00:25:59.386 --> 00:26:01.518 a few different publications.

NOTE Confidence: 0.313723

00:26:01.520 --> 00:26:03.236 It is more prevalent in women,

NOTE Confidence: 0.313723

00:26:03.240 --> 00:26:04.912 more prevalent in veterans,

NOTE Confidence: 0.313723

00:26:04.912 --> 00:26:08.120 and it is the only anxiety disorder

NOTE Confidence: 0.313723

00:26:08.120 --> 00:26:10.468 which predicts anxiety related

NOTE Confidence: 0.313723

00:26:10.468 --> 00:26:12.816 disorder which predicts suicidality

NOTE Confidence: 0.313723

00:26:12.816 --> 00:26:15.519 independent of other comorbidities.

NOTE Confidence: 0.313723

00:26:15.520 --> 00:26:18.240 Unfortunately, there are only two

NOTE Confidence: 0.313723

00:26:18.240 --> 00:26:20.960 FDA approved treatments for PTSD.

NOTE Confidence: 0.313723

00:26:20.960 --> 00:26:24.020 They're both SSRIs and they're both

NOTE Confidence: 0.313723

00:26:24.020 --> 00:26:27.280 developed for the treatment of depression.

NOTE Confidence: 0.313723

00:26:27.280 --> 00:26:29.160 So they have modest efficacy,

NOTE Confidence: 0.313723

00:26:29.160 --> 00:26:33.157 about 10% difference as compared to placebo,

NOTE Confidence: 0.313723

00:26:33.160 --> 00:26:36.260 smaller effect size than psychotherapy

NOTE Confidence: 0.313723

00:26:36.260 --> 00:26:39.360 and unclear synergy with psychotherapy.

NOTE Confidence: 0.313723

00:26:39.360 --> 00:26:43.424 They are slow to response typical to any

NOTE Confidence: 0.313723

00:26:43.424 --> 00:26:46.920 SSRIs of about, you know, two months.

NOTE Confidence: 0.313723

00:26:46.920 --> 00:26:47.824 And so you know,

NOTE Confidence: 0.313723

00:26:47.824 --> 00:26:49.560 we don't think that that's good enough,

NOTE Confidence: 0.313723

00:26:49.560 --> 00:26:50.033 right.

NOTE Confidence: 0.313723

00:26:50.033 --> 00:26:52.398 If somebody has severe symptoms,

NOTE Confidence: 0.313723

00:26:52.400 --> 00:26:53.273 they cannot sleep,

NOTE Confidence: 0.313723

00:26:53.273 --> 00:26:54.437 they cannot work etcetera,

NOTE Confidence: 0.313723

00:26:54.440 --> 00:26:54.745 etcetera.

NOTE Confidence: 0.313723

00:26:54.745 --> 00:26:57.880 You want to be able to help them right away.

NOTE Confidence: 0.313723

00:26:57.880 --> 00:27:00.301 And so there is a lot of data in

NOTE Confidence: 0.313723

00:27:00.301 --> 00:27:02.566 the literature showing that Anglo

NOTE Confidence: 0.313723

00:27:02.566 --> 00:27:05.440 5 is anxiolytic and could actually

NOTE Confidence: 0.313723

00:27:05.515 --> 00:27:08.360 participate in symptomatology of PTSD.

NOTE Confidence: 0.313723

00:27:08.360 --> 00:27:10.160 And all these data come

NOTE Confidence: 0.313723

00:27:10.160 --> 00:27:11.240 from preclinical models.

NOTE Confidence: 0.313723

00:27:11.240 --> 00:27:13.886 There are no data in human before

NOTE Confidence: 0.313723

00:27:13.886 --> 00:27:15.440 we started publishing this.

NOTE Confidence: 0.313723

00:27:15.440 --> 00:27:18.104 So we see that fear conditioning

NOTE Confidence: 0.313723

00:27:18.104 --> 00:27:19.880 is associated with increased

NOTE Confidence: 0.313723

00:27:19.957 --> 00:27:21.557 expression of Anglo 5.

NOTE Confidence: 0.313723

00:27:21.560 --> 00:27:24.362 Anglo 5 activity leads to enhancement

NOTE Confidence: 0.313723

00:27:24.362 --> 00:27:26.840 of contextual fear after stress.

NOTE Confidence: 0.313723

00:27:26.840 --> 00:27:29.678 Studies have shown that administration of

NOTE Confidence: 0.313723

00:27:29.678 --> 00:27:32.240 a negative Alastric modulator immediately

NOTE Confidence: 0.313723

00:27:32.240 --> 00:27:35.240 post trauma inhibits memory consolidation.

NOTE Confidence: 0.313723

00:27:35.240 --> 00:27:37.592 Our blockaded knockout of Anglo 5

NOTE Confidence: 0.313723

00:27:37.592 --> 00:27:39.160 interferes with fear extinction.

NOTE Confidence: 0.313723

00:27:39.160 --> 00:27:42.839 So these some of these seem against

NOTE Confidence: 0.313723

00:27:42.839 --> 00:27:44.751 each other And so we have to be

NOTE Confidence: 0.313723

00:27:44.751 --> 00:27:46.245 really careful of when we give

NOTE Confidence: 0.313723

00:27:46.245 --> 00:27:47.760 Anglo 5 to people with PTSD,

NOTE Confidence: 0.313723

00:27:47.760 --> 00:27:51.040 if we give it and whether we would

NOTE Confidence: 0.313723

00:27:51.040 --> 00:27:53.810 give agents directly targeting Anglo

NOTE Confidence: 0.313723

00:27:53.810 --> 00:27:57.360 5 or modulate via different pathway.

NOTE Confidence: 0.313723

00:27:57.360 --> 00:28:00.600 And so this is the first study that we did.

NOTE Confidence: 0.313723

00:28:00.600 --> 00:28:04.236 We recruited 16 individuals with PTSD.

NOTE Confidence: 0.313723

00:28:04.240 --> 00:28:07.000 They were all unmedicated, 16 age,

NOTE Confidence: 0.313723

00:28:07.000 --> 00:28:10.840 sex and smoking status match controls.

NOTE Confidence: 0.313723

00:28:10.840 --> 00:28:13.560 We did a lot of measures

NOTE Confidence: 0.313723

00:28:13.560 --> 00:28:16.360 including CAPS and and PCL,

NOTE Confidence: 0.313723

00:28:16.360 --> 00:28:18.384 which measured PTSD specifically.

NOTE Confidence: 0.313723

00:28:18.384 --> 00:28:22.375 And then all participants did a PET scan

NOTE Confidence: 0.313723

00:28:22.375 --> 00:28:24.800 to measure and glorify availability.

NOTE Confidence: 0.313723

00:28:24.800 --> 00:28:27.440 And so our sample was pretty chronic PTSD,

NOTE Confidence: 0.313723

00:28:27.440 --> 00:28:29.024 about 20 years.

NOTE Confidence: 0.313723

00:28:29.024 --> 00:28:30.080 On average,

NOTE Confidence: 0.313723

00:28:30.080 --> 00:28:32.198 nine met criteria for comorbid MDD,

NOTE Confidence: 0.313723

00:28:32.200 --> 00:28:34.825 which tells you that a lot of

NOTE Confidence: 0.313723

00:28:34.825 --> 00:28:36.703 these individuals were more severe

NOTE Confidence: 0.313723

00:28:36.703 --> 00:28:38.573 in their PTSD symptomatology.

NOTE Confidence: 0.313723

00:28:38.573 --> 00:28:42.520 It was a mixed trauma sample with some

NOTE Confidence: 0.313723

00:28:42.520 --> 00:28:44.720 civilians and some combat veterans.

NOTE Confidence: 0.313723

00:28:44.720 --> 00:28:47.464 And then we had six people with

NOTE Confidence: 0.313723

00:28:47.464 --> 00:28:49.023 passive suicidal ideations at

NOTE Confidence: 0.313723

00:28:49.023 --> 00:28:50.598 the time of pet scanning,

NOTE Confidence: 0.313723

00:28:50.600 --> 00:28:52.925 and four reported at least

NOTE Confidence: 0.313723

00:28:52.925 --> 00:28:54.320 one suicide attempt.

NOTE Confidence: 0.313723

00:28:54.320 --> 00:28:56.156 And so these are outcome data.

NOTE Confidence: 0.313723

00:28:56.160 --> 00:28:59.346 So the top panel is the

NOTE Confidence: 0.313723

00:28:59.346 --> 00:29:01.676 PTSD group and the bottom

NOTE Confidence: 0.78575593

00:29:01.680 --> 00:29:03.520 is our healthy control group.

NOTE Confidence: 0.78575593

00:29:03.520 --> 00:29:06.800 And so we look at, if you look at red,

NOTE Confidence: 0.78575593

00:29:06.800 --> 00:29:07.832 orange, yellow areas,

NOTE Confidence: 0.78575593

00:29:07.832 --> 00:29:10.240 these are quote UN quote hot areas.

NOTE Confidence: 0.78575593

00:29:10.240 --> 00:29:11.984 So these are the areas where we see

NOTE Confidence: 0.78575593

00:29:11.984 --> 00:29:13.667 the greatest density of whatever it is

NOTE Confidence: 0.78575593

00:29:13.667 --> 00:29:15.240 that you're trying to study in PET.

NOTE Confidence: 0.78575593

00:29:15.240 --> 00:29:17.184 And you can visually see higher

NOTE Confidence: 0.78575593

00:29:17.184 --> 00:29:18.480 receptor availability in people

NOTE Confidence: 0.78575593

00:29:18.531 --> 00:29:20.277 with PTSD as compared to controls.

NOTE Confidence: 0.78575593

00:29:20.280 --> 00:29:23.045 And that won't lie that we actually

NOTE Confidence: 0.78575593

00:29:23.045 --> 00:29:25.159 expected low receptor availability

NOTE Confidence: 0.78575593

00:29:25.159 --> 00:29:28.323 given the previous MDD study that

NOTE Confidence: 0.78575593

00:29:28.323 --> 00:29:31.209 was published and also thinking in

NOTE Confidence: 0.78575593

00:29:31.209 --> 00:29:33.520 terms of synaptic density and that

NOTE Confidence: 0.78575593

00:29:33.520 --> 00:29:35.860 it should be lower under stress

NOTE Confidence: 0.78575593

00:29:35.934 --> 00:29:38.154 disorders and so there should be

NOTE Confidence: 0.78575593

00:29:38.154 --> 00:29:40.318 less places from Glow 5 to sit.

NOTE Confidence: 0.78575593

00:29:40.320 --> 00:29:42.370 And so it would measure

NOTE Confidence: 0.78575593

00:29:42.370 --> 00:29:43.600 low receptor availability,

NOTE Confidence: 0.78575593

00:29:43.600 --> 00:29:47.156 but we showed crater across brain regions.

NOTE Confidence: 0.78575593

00:29:47.160 --> 00:29:49.424 And again prefrontal cortical

NOTE Confidence: 0.78575593

00:29:49.424 --> 00:29:51.622 regions were our main outcomes,

NOTE Confidence: 0.78575593

00:29:51.622 --> 00:29:55.072 but we saw this across the whole brain.

NOTE Confidence: 0.78575593

00:29:55.072 --> 00:29:57.856 And Sophie Holmes led the publication of

NOTE Confidence: 0.78575593

00:29:57.856 --> 00:30:00.880 this study and when she ran some correlation,

NOTE Confidence: 0.78575593

00:30:00.880 --> 00:30:03.040 she saw that high Anglo 5

NOTE Confidence: 0.78575593

00:30:03.040 --> 00:30:04.480 availability was associated with

NOTE Confidence: 0.78575593

00:30:04.548 --> 00:30:06.598 great avoidance symptoms in PTSD.

NOTE Confidence: 0.78575593

00:30:06.600 --> 00:30:09.127 So it's it's really interesting to see

NOTE Confidence: 0.78575593

00:30:09.127 --> 00:30:11.678 differences in the brains between groups,

NOTE Confidence: 0.78575593

00:30:11.680 --> 00:30:14.134 but it's actually much more interesting

NOTE Confidence: 0.78575593

00:30:14.134 --> 00:30:17.160 to see that there's clinical relevance.

NOTE Confidence: 0.78575593

00:30:17.160 --> 00:30:19.080 And this finding is really,

NOTE Confidence: 0.78575593

00:30:19.080 --> 00:30:21.592 really important because avoidance

NOTE Confidence: 0.78575593

00:30:21.592 --> 00:30:23.476 is something that

NOTE Confidence: 0.2830151

00:30:26.320 --> 00:30:28.100 prevents people from overcoming

NOTE Confidence: 0.2830151

00:30:28.100 --> 00:30:29.435 their PTSD symptoms.

NOTE Confidence: 0.2830151

00:30:29.440 --> 00:30:31.456 So if we avoid places, people, time,

NOTE Confidence: 0.2830151

00:30:31.456 --> 00:30:34.032 etcetera that remind us of the event,

NOTE Confidence: 0.2830151

00:30:34.040 --> 00:30:36.520 we cannot overcome the PTSD.

NOTE Confidence: 0.2830151

00:30:36.520 --> 00:30:38.422 And maybe on below 5 agents

NOTE Confidence: 0.2830151

00:30:38.422 --> 00:30:40.320 could help us with therapy,

NOTE Confidence: 0.2830151

00:30:40.320 --> 00:30:42.119 maybe we can give it prior to

NOTE Confidence: 0.2830151

00:30:42.119 --> 00:30:43.051 exposure therapy, etcetera.

NOTE Confidence: 0.2830151

00:30:43.051 --> 00:30:46.339 And again, I told you that I was

NOTE Confidence: 0.2830151

00:30:46.339 --> 00:30:49.560 kind of surprised by these findings.

NOTE Confidence: 0.2830151

00:30:49.560 --> 00:30:52.598 And so I had been collaborating with

NOTE Confidence: 0.2830151

00:30:52.598 --> 00:30:55.376 the late Ron Duman for some other work.

NOTE Confidence: 0.2830151

00:30:55.376 --> 00:30:57.589 And I had asked him if he could look

NOTE Confidence: 0.2830151

00:30:57.589 --> 00:30:59.443 at the postmortem brain tissue and

NOTE Confidence: 0.2830151

00:30:59.443 --> 00:31:01.610 people with PTSD that he had from

NOTE Confidence: 0.2830151

00:31:01.610 --> 00:31:03.841 National Center Brain Bank and see if

NOTE Confidence: 0.2830151

00:31:03.841 --> 00:31:05.923 there were Anglo 5 related proteins

NOTE Confidence: 0.2830151

00:31:05.923 --> 00:31:08.156 or stress related proteins that

NOTE Confidence: 0.2830151

00:31:08.156 --> 00:31:10.874 could help us explain his findings.

NOTE Confidence: 0.2830151

00:31:10.880 --> 00:31:13.712 And so Ron was kind to run some

NOTE Confidence: 0.2830151

00:31:13.712 --> 00:31:15.964 analysis for us and he showed that

NOTE Confidence: 0.2830151

00:31:15.964 --> 00:31:18.760 F KB P5 was 3 1/2 times lower and

NOTE Confidence: 0.2830151

00:31:18.760 --> 00:31:21.056 people with PTSD in the postmortem

NOTE Confidence: 0.2830151

00:31:21.056 --> 00:31:23.396 sample as compared to controls.

NOTE Confidence: 0.2830151

00:31:23.400 --> 00:31:26.340 And FKBP 5 is a glucocorticoid

NOTE Confidence: 0.2830151

00:31:26.340 --> 00:31:27.320 regulating protein.

NOTE Confidence: 0.2830151

00:31:27.320 --> 00:31:30.242 And there's some hypothesis that there's

NOTE Confidence: 0.2830151

00:31:30.242 --> 00:31:32.600 hypochlorosolamia in people with PTSD.

NOTE Confidence: 0.2830151

00:31:32.600 --> 00:31:35.664 So this would go along with just reduced

NOTE Confidence: 0.2830151

00:31:35.664 --> 00:31:37.917 cortisol tone in people with PTSD.

NOTE Confidence: 0.2830151

00:31:37.920 --> 00:31:40.475 And then he showed that Shank protein,

NOTE Confidence: 0.2830151

00:31:40.480 --> 00:31:43.240 but not Anglo 5 gene expression

NOTE Confidence: 0.2830151

00:31:43.240 --> 00:31:46.039 were higher in people with PTSD.

NOTE Confidence: 0.2830151

00:31:46.040 --> 00:31:47.240 And so again,

NOTE Confidence: 0.2830151

00:31:47.240 --> 00:31:49.240 what we're showing is lower

NOTE Confidence: 0.2830151

00:31:49.240 --> 00:31:51.503 cortisol protein but higher Anglo

NOTE Confidence: 0.2830151

00:31:51.503 --> 00:31:53.355 5 related trafficking protein.

NOTE Confidence: 0.2830151

00:31:53.360 --> 00:31:56.356 And So what we think is happening

NOTE Confidence: 0.2830151

00:31:56.360 --> 00:31:57.720 in the healthy brain,

NOTE Confidence: 0.2830151

00:31:57.720 --> 00:31:59.080 there's so many receptors,

NOTE Confidence: 0.2830151

00:31:59.080 --> 00:32:00.840 some of them are internalized,

NOTE Confidence: 0.2830151

00:32:00.840 --> 00:32:03.560 some of them are in the synaptic space.

NOTE Confidence: 0.2830151

00:32:03.560 --> 00:32:05.976 And so our radioligand as I told you

NOTE Confidence: 0.2830151

00:32:05.976 --> 00:32:08.944 can only bind to the places that to the

NOTE Confidence: 0.2830151

00:32:08.944 --> 00:32:11.280 receptors that are the synaptic space.

NOTE Confidence: 0.2830151

00:32:11.280 --> 00:32:12.126 In PTSD,

NOTE Confidence: 0.2830151

00:32:12.126 --> 00:32:14.241 we think that they're increased

NOTE Confidence: 0.2830151

00:32:14.241 --> 00:32:16.370 Shank levels which traffic Anglo

NOTE Confidence: 0.2830151

00:32:16.370 --> 00:32:18.320 5 to the synaptic space.

NOTE Confidence: 0.2830151

00:32:18.320 --> 00:32:20.510 Now the radioligand has more places

NOTE Confidence: 0.2830151

00:32:20.510 --> 00:32:22.624 to bind and so we're measuring

NOTE Confidence: 0.2830151

00:32:22.624 --> 00:32:24.354 receptor availability that is higher.

NOTE Confidence: 0.2830151

00:32:24.360 --> 00:32:26.680 So the number of receptors did not change,

NOTE Confidence: 0.2830151

00:32:26.680 --> 00:32:30.474 but their location changed and this location,

NOTE Confidence: 0.2830151

00:32:30.480 --> 00:32:33.186 this change in location appears to

NOTE Confidence: 0.2830151

00:32:33.186 --> 00:32:36.200 contribute to the avoided symptomatology.

NOTE Confidence: 0.2830151

00:32:36.200 --> 00:32:36.884 And so,

NOTE Confidence: 0.2830151

00:32:36.884 --> 00:32:38.594 given the higher rates of

NOTE Confidence: 0.2830151

00:32:38.594 --> 00:32:40.600 suicidality in this group as well,

NOTE Confidence: 0.2830151

00:32:40.600 --> 00:32:42.285 we proceeded with another study

NOTE Confidence: 0.2830151

00:32:42.285 --> 00:32:44.690 that was led by Maggie Davis.

NOTE Confidence: 0.2830151

00:32:44.690 --> 00:32:47.700 And we have people with who

NOTE Confidence: 0.2830151

00:32:47.700 --> 00:32:49.600 are healthy controls in grey,

NOTE Confidence: 0.2830151

00:32:49.600 --> 00:32:51.520 people with depression and purple.

NOTE Confidence: 0.2830151

00:32:51.520 --> 00:32:53.320 The light purple is people with

NOTE Confidence: 0.2830151

00:32:53.320 --> 00:32:55.202 depression who did not have suicidality

NOTE Confidence: 0.2830151

00:32:55.202 --> 00:32:57.074 at the time of pet scanning.

NOTE Confidence: 0.2830151

00:32:57.080 --> 00:33:00.032 And then the darker purple are people who

NOTE Confidence: 0.2830151

00:33:00.032 --> 00:33:02.398 had suicidality at the time of scanning.

NOTE Confidence: 0.2830151

00:33:02.400 --> 00:33:04.128 And then in below are people

NOTE Confidence: 0.2830151

00:33:04.128 --> 00:33:05.280 with PTSD and light.

NOTE Confidence: 0.2830151

00:33:05.280 --> 00:33:07.596 No suicidality time of scanning and

NOTE Confidence: 0.2830151

00:33:07.596 --> 00:33:09.959 then dark suicidality time of scanning.

NOTE Confidence: 0.2830151

00:33:09.960 --> 00:33:11.269 And so here I just wanted to

NOTE Confidence: 0.2830151

00:33:11.269 --> 00:33:12.520 show you our pretty images.

NOTE Confidence: 0.2830151

00:33:12.520 --> 00:33:15.348 So the top panel people with PTSD

NOTE Confidence: 0.2830151

00:33:15.348 --> 00:33:18.140 with suicidality and you can see

NOTE Confidence: 0.2830151

00:33:18.140 --> 00:33:19.625 significantly higher receptor

NOTE Confidence: 0.2830151

00:33:19.625 --> 00:33:21.540 availability in our graph and

NOTE Confidence: 0.2830151

00:33:21.540 --> 00:33:24.229 in this panel as compared to any

NOTE Confidence: 0.2830151

00:33:24.229 --> 00:33:26.599 other group in PTSD suicidality.

NOTE Confidence: 0.2830151

00:33:26.600 --> 00:33:29.040 And what was critically important

NOTE Confidence: 0.2830151

00:33:29.040 --> 00:33:30.992 is the correlation between

NOTE Confidence: 0.24639197

00:33:34.320 --> 00:33:37.572 and mood symptoms in people with

NOTE Confidence: 0.24639197

00:33:37.572 --> 00:33:39.840 depression as compared people with

NOTE Confidence: 0.24639197

00:33:39.840 --> 00:33:41.760 PTSD as compared to people with

NOTE Confidence: 0.24639197

00:33:41.760 --> 00:33:43.196 with depression were different.

NOTE Confidence: 0.24639197

00:33:43.196 --> 00:33:45.350 So people with PTSD who had

NOTE Confidence: 0.24639197

00:33:45.417 --> 00:33:47.205 greater receptor availability also

NOTE Confidence: 0.24639197

00:33:47.205 --> 00:33:49.440 had greater number of symptoms,

NOTE Confidence: 0.24639197

00:33:49.440 --> 00:33:51.270 but people with depression who

NOTE Confidence: 0.24639197

00:33:51.270 --> 00:33:53.233 had greater receptor availability

NOTE Confidence: 0.24639197

00:33:53.233 --> 00:33:55.357 had actually lower symptoms.

NOTE Confidence: 0.24639197

00:33:55.360 --> 00:33:56.824 So here again,

NOTE Confidence: 0.24639197

00:33:56.824 --> 00:34:00.300 we're using Anglo 5 to help us

NOTE Confidence: 0.24639197

00:34:00.300 --> 00:34:02.315 differentiate some stress disorders

NOTE Confidence: 0.24639197

00:34:02.315 --> 00:34:04.840 that may overlap in symptomatology

NOTE Confidence: 0.24639197

00:34:04.840 --> 00:34:07.033 and show that they really potentially

NOTE Confidence: 0.24639197

00:34:07.033 --> 00:34:09.798 need to be treated differently.

NOTE Confidence: 0.24639197

00:34:09.800 --> 00:34:13.112 But what I really was confused about and

NOTE Confidence: 0.24639197

00:34:13.112 --> 00:34:16.520 still wasn't explaining about these data was,

NOTE Confidence: 0.24639197

00:34:16.520 --> 00:34:20.055 is Anglo 5A regulation A

NOTE Confidence: 0.24639197

00:34:20.055 --> 00:34:22.365 predisposition to developing a PTSD?

NOTE Confidence: 0.24639197

00:34:22.365 --> 00:34:25.285 So are people who are born with high

NOTE Confidence: 0.24639197

00:34:25.285 --> 00:34:27.871 Anglo 5 levels are more likely to

NOTE Confidence: 0.24639197

00:34:27.871 --> 00:34:30.600 develop PTSD upon a traumatic event?

NOTE Confidence: 0.24639197

00:34:30.600 --> 00:34:33.020 Or is Anglo 5A regulation

NOTE Confidence: 0.24639197

00:34:33.020 --> 00:34:34.956 A consequence of PTSD?

NOTE Confidence: 0.24639197

00:34:34.960 --> 00:34:37.534 Because a lot of people have

NOTE Confidence: 0.24639197

00:34:37.534 --> 00:34:39.720 significant trauma in their life,

NOTE Confidence: 0.24639197

00:34:39.720 --> 00:34:42.720 but not all of them or most of

NOTE Confidence: 0.24639197

00:34:42.720 --> 00:34:45.640 them will develop PTSD symptoms.

NOTE Confidence: 0.24639197

00:34:45.640 --> 00:34:48.382 And so we collaborated with Jane

NOTE Confidence: 0.24639197

00:34:48.382 --> 00:34:51.529 Taylor and Ralph de Leon in

NOTE Confidence: 0.24639197

00:34:51.529 --> 00:34:54.104 Molecular Psychiatry and Ruth Ashe

NOTE Confidence: 0.24639197

00:34:54.104 --> 00:34:56.792 led the studies in animal models.

NOTE Confidence: 0.24639197

00:34:56.800 --> 00:34:58.116 They tried to do this in human,

NOTE Confidence: 0.24639197

00:34:58.120 --> 00:35:00.028 but it provided impossible to identify

NOTE Confidence: 0.24639197

00:35:00.028 --> 00:35:02.148 an emergency room people who had a

NOTE Confidence: 0.24639197

00:35:02.148 --> 00:35:03.463 traumatic event and then followed

NOTE Confidence: 0.24639197

00:35:03.463 --> 00:35:05.528 them for months to see if they would

NOTE Confidence: 0.24639197

00:35:05.528 --> 00:35:06.976 develop PTSD and scan everybody.

NOTE Confidence: 0.24639197

00:35:06.976 --> 00:35:10.624 And so Ruth took on the study in

NOTE Confidence: 0.24639197

00:35:10.624 --> 00:35:13.320 rats and we administered stress

NOTE Confidence: 0.24639197

00:35:13.320 --> 00:35:15.560 enhanced fear learning paradigm.

NOTE Confidence: 0.24639197

00:35:15.560 --> 00:35:17.558 And so after the animal survived,

NOTE Confidence: 0.24639197

00:35:17.560 --> 00:35:19.640 they acclimated for a bit.

NOTE Confidence: 0.24639197

00:35:19.640 --> 00:35:22.520 Then they participate in pet scanning,

NOTE Confidence: 0.24639197

00:35:22.520 --> 00:35:25.880 daily handling and then Ruth

NOTE Confidence: 0.24639197

00:35:25.880 --> 00:35:29.240 did behavioral testing and then

NOTE Confidence: 0.24639197

00:35:29.352 --> 00:35:30.546 more pet scanning.

NOTE Confidence: 0.24639197

00:35:30.546 --> 00:35:32.784 And so on the first day

NOTE Confidence: 0.24639197

00:35:32.784 --> 00:35:34.520 the animals were shocked

NOTE Confidence: 0.59004176

00:35:36.560 --> 00:35:38.765 and then the next day there was no shock

NOTE Confidence: 0.59004176

00:35:38.765 --> 00:35:40.862 in animals and they were shocked again

NOTE Confidence: 0.59004176

00:35:40.862 --> 00:35:43.398 the 3rd day and no shock on the 4th day.

NOTE Confidence: 0.59004176

00:35:43.400 --> 00:35:46.066 And so this is encephal paradigm

NOTE Confidence: 0.59004176

00:35:46.066 --> 00:35:49.196 where the shock is not,

NOTE Confidence: 0.59004176

00:35:49.200 --> 00:35:50.838 the number of shocks is not to

NOTE Confidence: 0.59004176

00:35:50.838 --> 00:35:52.465 the extent that all animals are

NOTE Confidence: 0.59004176

00:35:52.465 --> 00:35:54.199 going to develop PTC type symptoms,

NOTE Confidence: 0.59004176

00:35:54.200 --> 00:35:55.544 there's going to be a spread

NOTE Confidence: 0.59004176

00:35:55.544 --> 00:35:56.840 like just like in humans.

NOTE Confidence: 0.59004176

00:35:56.840 --> 00:35:59.552 So some animals are going to be resilient

NOTE Confidence: 0.59004176

00:35:59.552 --> 00:36:02.679 and some animals are going to be vulnerable.

NOTE Confidence: 0.59004176

00:36:02.680 --> 00:36:06.075 And we started seeing sex differences between

NOTE Confidence: 0.59004176

00:36:06.075 --> 00:36:08.838 behaviours in animals who were shocked.

NOTE Confidence: 0.54787356

00:36:11.360 --> 00:36:14.174 And then Ruth also divided the animals

NOTE Confidence: 0.54787356

00:36:14.174 --> 00:36:17.160 who were low responsers or resilient

NOTE Confidence: 0.54787356

00:36:17.160 --> 00:36:20.562 versus high responders or vulnerable after

NOTE Confidence: 0.54787356

00:36:20.562 --> 00:36:23.534 their shock in the in their freezing.

NOTE Confidence: 0.54787356

00:36:23.534 --> 00:36:25.824 And she saw sex differences

NOTE Confidence: 0.54787356

00:36:25.824 --> 00:36:28.080 in those groups as well.

NOTE Confidence: 0.54787356

00:36:28.080 --> 00:36:29.600 And then in PET scanning,

NOTE Confidence: 0.54787356

00:36:29.600 --> 00:36:32.360 we saw that actually receptor

NOTE Confidence: 0.54787356

00:36:32.360 --> 00:36:34.568 availability was not different

NOTE Confidence: 0.54787356

00:36:34.568 --> 00:36:37.124 between control groups and groups

NOTE Confidence: 0.54787356

00:36:37.124 --> 00:36:39.519 who were vulnerable or groups

NOTE Confidence: 0.54787356

00:36:39.519 --> 00:36:42.277 who develop PTSD type symptoms.

NOTE Confidence: 0.54787356

00:36:42.280 --> 00:36:44.596 So ANGLE 5 availability does not

NOTE Confidence: 0.54787356

00:36:44.596 --> 00:36:46.520 predispose to development of PTSD,

NOTE Confidence: 0.54787356

00:36:46.520 --> 00:36:48.080 at least in this work,

NOTE Confidence: 0.54787356

00:36:48.080 --> 00:36:50.520 but did increase in animals

NOTE Confidence: 0.54787356

00:36:50.520 --> 00:36:52.472 as a consequence of

NOTE Confidence: 0.4481057

00:36:54.640 --> 00:36:57.400 of foot shock of stress.

NOTE Confidence: 0.4481057

00:36:57.400 --> 00:37:00.410 And again we saw some stress sex

NOTE Confidence: 0.4481057

00:37:00.410 --> 00:37:02.185 differences And the freezing on day

NOTE Confidence: 0.4481057

00:37:02.185 --> 00:37:04.720 2 on the day that animals were not

NOTE Confidence: 0.4481057

00:37:04.720 --> 00:37:06.952 shocked is related to fear memory.

NOTE Confidence: 0.4481057

00:37:06.960 --> 00:37:09.865 So it's after the traumatic event when

NOTE Confidence: 0.4481057

00:37:09.865 --> 00:37:11.985 the animals are being put back in the

NOTE Confidence: 0.4481057

00:37:11.985 --> 00:37:13.895 context of where they were stressed and

NOTE Confidence: 0.4481057

00:37:13.895 --> 00:37:16.098 how do they behave there and how much

NOTE Confidence: 0.4481057

00:37:16.098 --> 00:37:17.684 freezing are they participating in.

NOTE Confidence: 0.4481057

00:37:17.684 --> 00:37:20.358 And so the greater the freezing behavior,

NOTE Confidence: 0.4481057

00:37:20.360 --> 00:37:23.000 the greater receptor availability and

NOTE Confidence: 0.4481057

00:37:23.000 --> 00:37:26.120 again some sex differences in that.

NOTE Confidence: 0.4481057

00:37:26.120 --> 00:37:30.720 And so looking at some more recent literature

NOTE Confidence: 0.4481057

00:37:30.720 --> 00:37:32.556 and back at some other literature,

NOTE Confidence: 0.4481057

00:37:32.560 --> 00:37:35.712 there is some evidence to support Anglo 5

NOTE Confidence: 0.4481057

00:37:35.712 --> 00:37:38.425 of regulation in response to PTSD events.

NOTE Confidence: 0.4481057

00:37:38.425 --> 00:37:40.910 And so this work was done right

NOTE Confidence: 0.4481057

00:37:40.992 --> 00:37:43.260 around the time that we published

NOTE Confidence: 0.4481057

00:37:43.260 --> 00:37:45.760 our work only in male models,

NOTE Confidence: 0.4481057

00:37:45.760 --> 00:37:48.935 but also showing that freezing

NOTE Confidence: 0.4481057

00:37:48.935 --> 00:37:52.370 behaviour is more prevalent in animals

NOTE Confidence: 0.4481057

00:37:52.370 --> 00:37:54.920 who develop PTSD type symptoms.

NOTE Confidence: 0.4481057

00:37:54.920 --> 00:37:57.594 But MPEP, which is Mglu 5 negative

NOTE Confidence: 0.4481057

00:37:57.594 --> 00:37:58.358 elastaric modulators,

NOTE Confidence: 0.4481057

00:37:58.360 --> 00:38:00.220 blocked this response,

NOTE Confidence: 0.4481057

00:38:00.220 --> 00:38:02.080 this freezing response.

NOTE Confidence: 0.4481057

00:38:02.080 --> 00:38:05.536 And actually animals also who had

NOTE Confidence: 0.4481057

00:38:05.536 --> 00:38:08.834 greater PTSD symptoms had developed more,

NOTE Confidence: 0.4481057

00:38:08.834 --> 00:38:12.313 had greater Mglu 5 availability upon retest.

NOTE Confidence: 0.4481057

00:38:12.320 --> 00:38:14.876 But MPEP had blocked this effect.

NOTE Confidence: 0.4481057

00:38:14.880 --> 00:38:16.372 So the study actually,

NOTE Confidence: 0.4481057

00:38:16.372 --> 00:38:17.118 you know,

NOTE Confidence: 0.4481057

00:38:17.120 --> 00:38:19.620 did some treatment and showed

NOTE Confidence: 0.4481057

00:38:19.620 --> 00:38:22.560 that treatment with Mglu 5 NAMM

NOTE Confidence: 0.4481057

00:38:22.560 --> 00:38:24.512 could actually be beneficial.

NOTE Confidence: 0.4481057

00:38:24.520 --> 00:38:27.976 And so we also did our own work

NOTE Confidence: 0.4481057

00:38:27.976 --> 00:38:31.120 to modulate Mglo 5 to see we'll

NOTE Confidence: 0.4481057

00:38:31.120 --> 00:38:33.399 change symptomatology in human.

NOTE Confidence: 0.59582347

00:38:36.280 --> 00:38:38.345 And we did this a while ago

NOTE Confidence: 0.59582347

00:38:38.345 --> 00:38:40.878 via administration of ketamine.

NOTE Confidence: 0.59582347

00:38:40.878 --> 00:38:44.860 And why we administered ketamine is we

NOTE Confidence: 0.59582347

00:38:44.860 --> 00:38:48.136 wanted to modulate Mglo 5 not directly,

NOTE Confidence: 0.59582347

00:38:48.136 --> 00:38:50.876 but via modulation of glutamate.

NOTE Confidence: 0.59582347

00:38:50.880 --> 00:38:53.553 And I think all of you know at this

NOTE Confidence: 0.59582347

00:38:53.553 --> 00:38:55.978 point that 7 acetic doses of ketamine

NOTE Confidence: 0.59582347

00:38:55.978 --> 00:38:58.799 lead to a large surge in glutamate.

NOTE Confidence: 0.59582347

00:38:58.800 --> 00:39:00.996 This was replicated many, many times,

NOTE Confidence: 0.59582347

00:39:01.000 --> 00:39:02.440 but anaesthetic doses do not

NOTE Confidence: 0.59582347

00:39:02.440 --> 00:39:04.560 lead to a surge in glutamate.

NOTE Confidence: 0.59582347

00:39:04.560 --> 00:39:08.200 And there were studies done with Mrs.

NOTE Confidence: 0.59582347

00:39:08.200 --> 00:39:10.200 showing this is proton, Mrs.

NOTE Confidence: 0.59582347

00:39:10.200 --> 00:39:12.080 showing that administration of ketamine

NOTE Confidence: 0.59582347

00:39:12.080 --> 00:39:14.852 leads to increases in glutamate in human.

NOTE Confidence: 0.59582347

00:39:14.852 --> 00:39:17.528 And then Jerry Senecora and his

NOTE Confidence: 0.59582347

00:39:17.528 --> 00:39:21.264 group did a study with carbon 13 Mrs.

NOTE Confidence: 0.59582347

00:39:21.264 --> 00:39:23.408 showing increases in glutamate

NOTE Confidence: 0.59582347

00:39:23.408 --> 00:39:25.656 levels after anesthetic doses

NOTE Confidence: 0.59582347

00:39:25.656 --> 00:39:28.596 of ketamine in animal models.

NOTE Confidence: 0.59582347

00:39:28.600 --> 00:39:31.274 And so this was our study day,

NOTE Confidence: 0.59582347

00:39:31.280 --> 00:39:32.588 our study design, sorry.

NOTE Confidence: 0.59582347

00:39:32.588 --> 00:39:34.550 So we screened subjects and they

NOTE Confidence: 0.59582347

00:39:34.610 --> 00:39:36.396 participate in MRI scanning and

NOTE Confidence: 0.59582347

00:39:36.396 --> 00:39:38.048 then we do a baseline scan and

NOTE Confidence: 0.59582347

00:39:38.048 --> 00:39:39.519 a ketamine scan the same day.

NOTE Confidence: 0.59582347

00:39:39.520 --> 00:39:41.956 And then we invited people 24 hours

NOTE Confidence: 0.59582347

00:39:41.956 --> 00:39:43.689 later to participate in another

NOTE Confidence: 0.59582347

00:39:43.689 --> 00:39:45.920 scan and we picked the 24 hour

NOTE Confidence: 0.59582347

00:39:45.920 --> 00:39:48.332 time point is because that's the

NOTE Confidence: 0.59582347

00:39:48.332 --> 00:39:50.030 greatest antidepressant response

NOTE Confidence: 0.59582347

00:39:50.030 --> 00:39:51.560 of ketamine administration.

NOTE Confidence: 0.59582347

00:39:51.560 --> 00:39:54.386 And so we thought that administration

NOTE Confidence: 0.59582347

00:39:54.386 --> 00:39:56.942 of ketamine would lead to a

NOTE Confidence: 0.59582347

00:39:56.942 --> 00:39:59.137 glutamate surge which would down

NOTE Confidence: 0.59582347

00:39:59.137 --> 00:40:01.040 regulate and Glu fives immediately.

NOTE Confidence: 0.59582347

00:40:01.040 --> 00:40:03.691 But that would lead to an up

NOTE Confidence: 0.59582347

00:40:03.691 --> 00:40:05.825 regulation of Glu 524 hours later

NOTE Confidence: 0.59582347

00:40:05.825 --> 00:40:07.955 because there will be more synapses.

NOTE Confidence: 0.59582347

00:40:07.960 --> 00:40:10.996 Given Ron's work of increased synaptogenesis,

NOTE Confidence: 0.59582347

00:40:11.000 --> 00:40:13.920 there will be more synapses.

NOTE Confidence: 0.59582347

00:40:13.920 --> 00:40:15.720 More places for Anglo 5 to sit on

NOTE Confidence: 0.59582347

00:40:15.720 --> 00:40:18.055 and so there will be greater angle 5

NOTE Confidence: 0.59582347

00:40:18.055 --> 00:40:20.141 availability and it will be related

NOTE Confidence: 0.59582347

00:40:20.141 --> 00:40:22.482 to instepressing response and so on.

NOTE Confidence: 0.59582347

00:40:22.482 --> 00:40:23.978 The ketamine day subjects

NOTE Confidence: 0.59582347

00:40:23.978 --> 00:40:25.560 participating to PET scans.

NOTE Confidence: 0.59582347

00:40:25.560 --> 00:40:26.880 That radio tracer was

NOTE Confidence: 0.59582347

00:40:26.880 --> 00:40:28.200 administered as a bolus,

NOTE Confidence: 0.59582347

00:40:28.200 --> 00:40:30.756 People are scanned for 90 minutes,

NOTE Confidence: 0.59582347

00:40:30.760 --> 00:40:33.256 they had a break and then we administered

NOTE Confidence: 0.59582347

00:40:33.256 --> 00:40:35.691 the radio tracer followed by ketamine

NOTE Confidence: 0.59582347

00:40:35.691 --> 00:40:37.435 bolus plus infusion paradigm.

NOTE Confidence: 0.59582347

00:40:37.440 --> 00:40:39.500 So this administration gives a

NOTE Confidence: 0.59582347

00:40:39.500 --> 00:40:42.666 bit more ketamine than the quote

NOTE Confidence: 0.59582347

00:40:42.666 --> 00:40:45.952 typical antidepressant 40 minute

NOTE Confidence: 0.59582347

00:40:45.952 --> 00:40:47.560 just infusion administration.

NOTE Confidence: 0.59582347

00:40:47.560 --> 00:40:51.093 But we really given the expense of pet,

NOTE Confidence: 0.59582347

00:40:51.093 --> 00:40:52.758 the need for a line,

NOTE Confidence: 0.59582347

00:40:52.760 --> 00:40:55.063 the radiation we give the subjects the

NOTE Confidence: 0.59582347

00:40:55.063 --> 00:40:57.639 time the subjects contribute to our studies.

NOTE Confidence: 0.59582347

00:40:57.640 --> 00:40:59.992 We really wanted to make sure that

NOTE Confidence: 0.59582347

00:40:59.992 --> 00:41:02.185 we're going to see significant findings

NOTE Confidence: 0.59582347

00:41:02.185 --> 00:41:04.160 if there were significant findings.

NOTE Confidence: 0.59582347

00:41:04.160 --> 00:41:06.437 So we gave a bit of a higher dose.

NOTE Confidence: 0.59582347

00:41:06.440 --> 00:41:09.500 So we had 13 people with

NOTE Confidence: 0.59582347

00:41:09.500 --> 00:41:10.520 depression participate.

NOTE Confidence: 0.59582347

00:41:10.520 --> 00:41:13.238 They you can see that they're

NOTE Confidence: 0.59582347

00:41:13.240 --> 00:41:15.034 depression scores were a bit lower

NOTE Confidence: 0.59582347

00:41:15.034 --> 00:41:16.512 than the typical depression group

NOTE Confidence: 0.59582347

00:41:16.512 --> 00:41:18.272 that we recruit but we were excluding

NOTE Confidence: 0.59582347

00:41:18.272 --> 00:41:19.840 people with any suicidality.

NOTE Confidence: 0.59582347

00:41:19.840 --> 00:41:21.360 We were really, really,

NOTE Confidence: 0.59582347

00:41:21.360 --> 00:41:23.074 really careful about making sure

NOTE Confidence: 0.59582347

00:41:23.074 --> 00:41:24.664 that people who are participating

NOTE Confidence: 0.59582347

00:41:24.664 --> 00:41:26.781 in the study given there was a

NOTE Confidence: 0.59582347

00:41:26.781 --> 00:41:28.811 research study with only one dose of

NOTE Confidence: 0.59582347

00:41:28.811 --> 00:41:30.932 ketamine and no treatment after that.

NOTE Confidence: 0.59582347

00:41:30.932 --> 00:41:33.856 We followed subjects but we did not

NOTE Confidence: 0.59582347

00:41:33.856 --> 00:41:35.664 provide treatment pharmacological treatment.

NOTE Confidence: 0.59582347

00:41:35.664 --> 00:41:38.548 We really wanted to make sure that

NOTE Confidence: 0.59582347

00:41:38.548 --> 00:41:40.800 these were subjects who could be

NOTE Confidence: 0.59582347

00:41:40.800 --> 00:41:43.003 able to complete the study without

NOTE Confidence: 0.59582347

00:41:43.003 --> 00:41:45.421 adverse events and then we have

NOTE Confidence: 0.59582347

00:41:45.421 --> 00:41:47.480 13 match controls as typical.

NOTE Confidence: 0.59582347

00:41:47.480 --> 00:41:50.558 And so this is our preliminary,

NOTE Confidence: 0.59582347

00:41:50.560 --> 00:41:51.658 our first study.

NOTE Confidence: 0.59582347

00:41:51.658 --> 00:41:54.220 This was only in healthy controls that

NOTE Confidence: 0.7197303

00:41:54.293 --> 00:41:57.158 Chrissy published in Biological Psychiatry.

NOTE Confidence: 0.7197303

00:41:57.160 --> 00:42:00.240 And so the top panel is MRI scans,

NOTE Confidence: 0.7197303

00:42:00.240 --> 00:42:02.968 the middle panel is our baseline PET and

NOTE Confidence: 0.7197303

00:42:02.968 --> 00:42:05.599 the bottom panel is our ketamine study.

NOTE Confidence: 0.7197303

00:42:05.600 --> 00:42:07.475 And you can see significant

NOTE Confidence: 0.7197303

00:42:07.475 --> 00:42:08.975 decrease in receptor availability

NOTE Confidence: 0.7197303

00:42:08.975 --> 00:42:10.920 after administration of ketamine.

NOTE Confidence: 0.7197303

00:42:10.920 --> 00:42:13.472 And if you think back to slide maybe

NOTE Confidence: 0.7197303

00:42:13.472 --> 00:42:17.056 8 or 9 where I showed you there are no

NOTE Confidence: 0.7197303

00:42:17.056 --> 00:42:19.824 variation of Unglu 5 and that in the

NOTE Confidence: 0.7197303

00:42:19.824 --> 00:42:22.680 afternoon Unglu 5 levels are lower as it is.

NOTE Confidence: 0.7197303

00:42:22.680 --> 00:42:23.700 Given that we were measuring

NOTE Confidence: 0.7197303

00:42:23.700 --> 00:42:24.516 this in the afternoon,

NOTE Confidence: 0.7197303

00:42:24.520 --> 00:42:30.408 we're likely sub estimating how much display,

NOTE Confidence: 0.7197303

00:42:30.408 --> 00:42:32.616 how much change there was after

NOTE Confidence: 0.7197303

00:42:32.616 --> 00:42:33.720 administration of ketamine.

NOTE Confidence: 0.7197303

00:42:33.720 --> 00:42:36.760 So this 20 to 40% change the way measured,

NOTE Confidence: 0.7197303

00:42:36.760 --> 00:42:38.440 it's probably even greater.

NOTE Confidence: 0.7197303

00:42:38.440 --> 00:42:41.107 And this was across all brain regions

NOTE Confidence: 0.7197303

00:42:41.107 --> 00:42:42.662 including the cerebellum where

NOTE Confidence: 0.7197303

00:42:42.662 --> 00:42:44.720 people use as a reference tissue,

NOTE Confidence: 0.7197303

00:42:44.720 --> 00:42:47.125 again providing evidence that there

NOTE Confidence: 0.7197303

00:42:47.125 --> 00:42:50.231 is really indeed no reference tissue

NOTE Confidence: 0.7197303

00:42:50.231 --> 00:42:52.719 for measuring anglify availability.

NOTE Confidence: 0.7197303

00:42:52.720 --> 00:42:57.640 And contrary to our initial hypothesis,

NOTE Confidence: 0.7197303

00:42:57.640 --> 00:43:00.440 the 24 hour PET scan here in Gray,

NOTE Confidence: 0.7197303

00:43:00.440 --> 00:43:03.870 we're showing persistent lower Anglify

NOTE Confidence: 0.7197303

00:43:03.870 --> 00:43:06.830 availability and people with who are

NOTE Confidence: 0.7197303

00:43:06.830 --> 00:43:10.439 controls and and people who are depressed.

NOTE Confidence: 0.7197303

00:43:10.440 --> 00:43:14.222 And so again we were surprised and

NOTE Confidence: 0.7197303

00:43:14.222 --> 00:43:16.732 given that we expected increases

NOTE Confidence: 0.7197303

00:43:16.732 --> 00:43:18.793 in Anglophile availability and

NOTE Confidence: 0.7197303

00:43:18.793 --> 00:43:21.558 all of the initial studies,

NOTE Confidence: 0.7197303

00:43:21.560 --> 00:43:23.996 the mechanistic studies that I showed you

NOTE Confidence: 0.7197303

00:43:24.000 --> 00:43:26.758 helped us understand what is going on.

NOTE Confidence: 0.7197303

00:43:26.760 --> 00:43:29.955 And so on the left we have a typical

NOTE Confidence: 0.7197303

00:43:29.955 --> 00:43:32.640 situation where person has had no drug.

NOTE Confidence: 0.7197303

00:43:32.640 --> 00:43:34.365 Some of the receptors are

NOTE Confidence: 0.7197303

00:43:34.365 --> 00:43:35.400 the extrasynaptic space.

NOTE Confidence: 0.7197303

00:43:35.400 --> 00:43:38.403 There's so much glutamate and we're measuring

NOTE Confidence: 0.7197303

00:43:38.403 --> 00:43:41.437 receptors that are here on the cell surface.

NOTE Confidence: 0.7197303

00:43:41.440 --> 00:43:41.824 However,

NOTE Confidence: 0.7197303

00:43:41.824 --> 00:43:43.360 after administration of ketamine,

NOTE Confidence: 0.7197303

00:43:43.360 --> 00:43:45.466 we think there's greater glutamate release

NOTE Confidence: 0.7197303

00:43:45.466 --> 00:43:48.517 which is going to down regulate on Glu fives.

NOTE Confidence: 0.7197303

00:43:48.520 --> 00:43:50.207 So now more on Glu fives are

NOTE Confidence: 0.7197303

00:43:50.207 --> 00:43:52.080 going to be an internal space.

NOTE Confidence: 0.7197303

00:43:52.080 --> 00:43:54.342 Given that the radio ligand cannot

NOTE Confidence: 0.7197303

00:43:54.342 --> 00:43:55.473 measure internalized receptors,

NOTE Confidence: 0.7197303

00:43:55.480 --> 00:43:58.120 we're measuring low receptor availability.

NOTE Confidence: 0.7197303

00:43:58.120 --> 00:44:00.838 So we're thinking that this low

NOTE Confidence: 0.7197303

00:44:00.838 --> 00:44:02.650 receptor availability is indeed

NOTE Confidence: 0.7197303

00:44:02.722 --> 00:44:05.208 receptor trafficking to the

NOTE Confidence: 0.7197303

00:44:05.208 --> 00:44:07.828 internalized space and potentially is

NOTE Confidence: 0.7197303

00:44:07.828 --> 00:44:10.560 associated with changes in hematology.

NOTE Confidence: 0.7197303

00:44:10.560 --> 00:44:13.115 And so of course they told you

NOTE Confidence: 0.7197303

00:44:13.115 --> 00:44:13.719 to me it's really,

NOTE Confidence: 0.7197303

00:44:13.720 --> 00:44:15.845 really important to understand the

NOTE Confidence: 0.7197303

00:44:15.845 --> 00:44:17.970 link between what we're seeing

NOTE Confidence: 0.7197303

00:44:18.043 --> 00:44:19.678 in the brain to symptoms.

NOTE Confidence: 0.7197303

00:44:19.680 --> 00:44:22.554 And we saw a significant association

NOTE Confidence: 0.7197303

00:44:22.554 --> 00:44:25.599 between decreased and Angle 5 availability

NOTE Confidence: 0.7197303

00:44:25.600 --> 00:44:27.835 and decrease in symptomatology in

NOTE Confidence: 0.7197303

00:44:27.835 --> 00:44:30.760 specific in the psychic anxiety symptoms.

NOTE Confidence: 0.7197303

00:44:30.760 --> 00:44:34.964 And we also saw a decrease in suicidality

NOTE Confidence: 0.7197303

00:44:34.964 --> 00:44:37.974 in individuals who had greater

NOTE Confidence: 0.7197303

00:44:37.974 --> 00:44:41.319 decrease in Angle 5 availability.

NOTE Confidence: 0.7197303

00:44:41.320 --> 00:44:45.340 And so between the PTSD study

NOTE Confidence: 0.7197303

00:44:45.340 --> 00:44:48.056 and this ketamine study,

NOTE Confidence: 0.7197303

00:44:48.056 --> 00:44:51.420 we are seeing the Anglo 5 May

NOTE Confidence: 0.7197303

00:44:51.420 --> 00:44:53.045 not only help us differentiate

NOTE Confidence: 0.7197303

00:44:53.045 --> 00:44:54.639 between different disorders,

NOTE Confidence: 0.7197303

00:44:54.640 --> 00:44:57.237 but potentially has a role in suicidality.

NOTE Confidence: 0.7197303

00:44:57.240 --> 00:44:59.214 And I'm also seeing some of this

NOTE Confidence: 0.7197303

00:44:59.214 --> 00:45:01.322 in my bipolar work that I'm not

NOTE Confidence: 0.7197303

00:45:01.322 --> 00:45:02.518 ready to present yet.

NOTE Confidence: 0.7197303

00:45:02.520 --> 00:45:05.040 But going back to the literature,

NOTE Confidence: 0.7197303

00:45:05.040 --> 00:45:05.880 there's some

NOTE Confidence: 0.44133765

00:45:08.200 --> 00:45:10.916 support for alterations in Homer which is

NOTE Confidence: 0.44133765

00:45:10.916 --> 00:45:12.759 another trafficking protein for Anglo 5

NOTE Confidence: 0.44133765

00:45:12.760 --> 00:45:15.478 which is associated with suicide attempt.

NOTE Confidence: 0.44133765

00:45:15.480 --> 00:45:19.440 Higher PSD and 95 levels which is a

NOTE Confidence: 0.44133765

00:45:19.440 --> 00:45:22.800 post synaptic protein is a is increased

NOTE Confidence: 0.44133765

00:45:22.800 --> 00:45:25.792 in people with who died by suicide.

NOTE Confidence: 0.44133765

00:45:25.792 --> 00:45:27.732 Both ketamine and lithium exert

NOTE Confidence: 0.44133765

00:45:27.732 --> 00:45:30.414 into suicidal actions via influences

NOTE Confidence: 0.44133765

00:45:30.414 --> 00:45:32.079 and glutamatergic system.

NOTE Confidence: 0.44133765

00:45:32.080 --> 00:45:34.376 And now we're having evidence from our

NOTE Confidence: 0.44133765

00:45:34.376 --> 00:45:36.863 group showing that greater extent of

NOTE Confidence: 0.44133765

00:45:36.863 --> 00:45:39.869 Glu 5 down regulation is supporting

NOTE Confidence: 0.44133765

00:45:39.869 --> 00:45:42.919 greater relief from suicidal thinking.

NOTE Confidence: 0.44133765

00:45:42.920 --> 00:45:45.624 And so I truly believe that M Glu

NOTE Confidence: 0.44133765

00:45:45.624 --> 00:45:49.297 5 is an important agent to study in

NOTE Confidence: 0.44133765

00:45:49.297 --> 00:45:51.782 helping us alleviate mental illness

NOTE Confidence: 0.44133765

00:45:51.782 --> 00:45:54.206 in various populations and there

NOTE Confidence: 0.44133765

00:45:54.206 --> 00:45:56.290 could be differentially expressed

NOTE Confidence: 0.44133765

00:45:56.290 --> 00:45:59.030 and differentially important across

NOTE Confidence: 0.44133765

00:45:59.030 --> 00:46:00.400 different populations.

NOTE Confidence: 0.44133765

00:46:00.400 --> 00:46:02.720 And this is all I have to show

NOTE Confidence: 0.44133765

00:46:02.720 --> 00:46:04.639 in terms of my large data,

NOTE Confidence: 0.44133765

00:46:04.640 --> 00:46:08.276 but I did want to show you a couple,

NOTE Confidence: 0.44133765

00:46:08.280 --> 00:46:11.800 just a couple more slides that have been,

NOTE Confidence: 0.44133765

00:46:11.800 --> 00:46:14.170 this is secondary analysis from what

NOTE Confidence: 0.44133765

00:46:14.170 --> 00:46:16.691 we've been doing and I'm looking

NOTE Confidence: 0.44133765

00:46:16.691 --> 00:46:18.435 for some collaborators especially

NOTE Confidence: 0.44133765

00:46:18.435 --> 00:46:20.600 in the studies of pain.

NOTE Confidence: 0.44133765

00:46:20.600 --> 00:46:23.678 So a lot of, you know,

NOTE Confidence: 0.44133765

00:46:23.680 --> 00:46:24.568 you know,

NOTE Confidence: 0.44133765

00:46:24.568 --> 00:46:26.788 there's interplay between pain and

NOTE Confidence: 0.44133765

00:46:26.788 --> 00:46:27.676 mood symptoms,

NOTE Confidence: 0.44133765

00:46:27.680 --> 00:46:30.398 but also between pain and suicidality.

NOTE Confidence: 0.44133765

00:46:30.400 --> 00:46:32.927 And what we're seeing with our Angular

NOTE Confidence: 0.44133765

00:46:32.927 --> 00:46:36.283 5 work in people is higher receptor

NOTE Confidence: 0.44133765

00:46:36.283 --> 00:46:37.930 availability across diagnostic

NOTE Confidence: 0.44133765

00:46:37.930 --> 00:46:40.874 groups in people who reported chronic

NOTE Confidence: 0.44133765

00:46:40.874 --> 00:46:43.716 pain at the time of PET scanning.

NOTE Confidence: 0.44133765

00:46:43.720 --> 00:46:45.477 So they're in the top panel as

NOTE Confidence: 0.44133765

00:46:45.477 --> 00:46:47.039 compared to healthy control groups.

NOTE Confidence: 0.44133765

00:46:47.040 --> 00:46:49.630 And I just showed you that suicidality

NOTE Confidence: 0.44133765

00:46:49.630 --> 00:46:51.632 is associated with higher angular

NOTE Confidence: 0.44133765

00:46:51.632 --> 00:46:53.276 5 availability as well.

NOTE Confidence: 0.44133765

00:46:53.280 --> 00:46:56.092 And so, you know, I'm,

NOTE Confidence: 0.44133765

00:46:56.092 --> 00:46:58.360 I'm trying to see if I can study

NOTE Confidence: 0.44133765

00:46:58.360 --> 00:47:00.360 pain and suicidality simultaneously,

NOTE Confidence: 0.44133765

00:47:00.360 --> 00:47:01.491 potentially cross diagnosis.

NOTE Confidence: 0.44133765

00:47:01.491 --> 00:47:02.999 And if anybody's interested,

NOTE Confidence: 0.44133765

00:47:03.000 --> 00:47:04.688 please let me know.

NOTE Confidence: 0.44133765

00:47:04.688 --> 00:47:07.220 But what is also really important

NOTE Confidence: 0.44133765

00:47:07.303 --> 00:47:09.691 is our pilot data showing higher

NOTE Confidence: 0.44133765

00:47:09.691 --> 00:47:12.741 Anglo 5 levels in people who use

NOTE Confidence: 0.44133765

00:47:12.741 --> 00:47:14.460 cannabis as compared to people

NOTE Confidence: 0.44133765

00:47:14.460 --> 00:47:16.035 who do not use cannabis.

NOTE Confidence: 0.44133765

00:47:16.040 --> 00:47:17.432 And I know a lot of people use

NOTE Confidence: 0.44133765

00:47:17.432 --> 00:47:18.718 cannabis and report using cannabis.

NOTE Confidence: 0.44133765

00:47:18.720 --> 00:47:22.960 And again, this is across stress groups.

NOTE Confidence: 0.44133765

00:47:22.960 --> 00:47:24.612 People call us and they say they

NOTE Confidence: 0.44133765

00:47:24.612 --> 00:47:26.018 use cannabis to relieve their

NOTE Confidence: 0.44133765

00:47:26.018 --> 00:47:27.618 PTSD symptoms or their anxiety

NOTE Confidence: 0.44133765

00:47:27.618 --> 00:47:29.080 symptoms or whatever symptoms,

NOTE Confidence: 0.44133765

00:47:29.080 --> 00:47:30.223 their pain symptoms.

NOTE Confidence: 0.44133765

00:47:30.223 --> 00:47:32.890 But it appears that use of cannabis

NOTE Confidence: 0.44133765

00:47:32.964 --> 00:47:35.280 is actually up regulating MGULA 5,

NOTE Confidence: 0.44133765

00:47:35.280 --> 00:47:36.875 which may potentially put these

NOTE Confidence: 0.44133765

00:47:36.875 --> 00:47:39.200 people at higher risk for suicidality.

NOTE Confidence: 0.44133765

00:47:39.200 --> 00:47:40.838 So I just wanted to show this,

NOTE Confidence: 0.44133765

00:47:40.840 --> 00:47:43.817 it's all preliminary data that

NOTE Confidence: 0.44133765

00:47:43.817 --> 00:47:45.359 we we're playing around with to

NOTE Confidence: 0.44133765

00:47:45.359 --> 00:47:47.039 see what we're going to do next.

NOTE Confidence: 0.44133765

00:47:47.040 --> 00:47:48.906 And if anybody wants to work

NOTE Confidence: 0.44133765

00:47:48.906 --> 00:47:50.488 together to collaborate, let me know.

NOTE Confidence: 0.44133765

00:47:50.488 --> 00:47:52.560 And thank you so much for your attention.

NOTE Confidence: 0.32573488

00:47:59.560 --> 00:48:00.280 Thanks, Irena.