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
- $00:00:05.480 \longrightarrow 00:00:06.240$ Yeah. Thank you so much,
- NOTE Confidence: 0.71403414
- $00:00:06.240 \longrightarrow 00:00:09.400$ Jerry, for the introduction.
- NOTE Confidence: 0.71403414
- $00{:}00{:}09{.}400 \dashrightarrow 00{:}00{:}12.048$ 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
- $00:00:14.440 \longrightarrow 00:00:16.190$ And it actually started in
- NOTE Confidence: 0.71403414
- $00:00:16.190 \longrightarrow 00:00:17.240$ 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
- $00{:}00{:}22.200 \dashrightarrow 00{:}00{:}24.288$ 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
- $00:00:25.680 \dashrightarrow 00:00:29.170$ but I'd be happy to come back and another
- NOTE Confidence: 0.71403414
- $00{:}00{:}29{.}170 \dashrightarrow 00{:}00{:}31{.}960$ grand rounds and talk about that.
- NOTE Confidence: 0.71403414

 $00:00:31.960 \longrightarrow 00:00:34.655$ So if you guys know it takes

NOTE Confidence: 0.71403414

 $00{:}00{:}34.655 \dashrightarrow 00{:}00{:}37.199$ an army to do this work,

NOTE Confidence: 0.71403414

 $00:00:37.200 \longrightarrow 00:00:38.887$ this is some of the army that

NOTE Confidence: 0.71403414

 $00:00:38.887 \longrightarrow 00:00:40.399$ has helped me do this work.

NOTE Confidence: 0.71403414

 $00{:}00{:}40{.}400 \dashrightarrow 00{:}00{:}43{.}001$ 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

 $00{:}00{:}45{.}440 \dashrightarrow 00{:}00{:}47{.}555$ And these are the acknowledgements

NOTE Confidence: 0.71403414

 $00:00:47.555 \rightarrow 00:00:49.670$ 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-->00:00:55.288Sarah 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

 $00:00:57.325 \dashrightarrow 00:00:58.673$ and identification of subjects.

NOTE Confidence: 0.71403414

 $00{:}00{:}58.680 \dashrightarrow 00{:}01{:}00.990$ And then Rich Carson has been my

NOTE Confidence: 0.71403414

 $00:01:00.990 \rightarrow 00:01:03.318$ 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

 $00:01:04.580 \longrightarrow 00:01:06.154$ has done a lot of ketamine.

- NOTE Confidence: 0.71403414
- $00:01:06.154 \rightarrow 00:01:09.147$ I'm go 5 work with me and Jane Taylor,

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

NOTE Confidence: 0.71403414

 $00:01:10.992 \longrightarrow 00:01:12.957$ have really helped a lot through

NOTE Confidence: 0.71403414

 $00:01:12.960 \longrightarrow 00:01:15.760$ 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

 $00:01:19.000 \longrightarrow 00:01:20.080$ 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

 $00:01:22.888 \rightarrow 00:01:25.318$ glutamate besides the fact that we

NOTE Confidence: 0.71403414

 $00{:}01{:}25{.}318 \dashrightarrow 00{:}01{:}26{.}974$ can actually image gluta matergic

NOTE Confidence: 0.71403414

 $00:01:26.974 \rightarrow 00:01:29.279$ system in the brain in humans?

NOTE Confidence: 0.71403414

 $00:01:29.280 \longrightarrow 00:01:29.644$ Well,

NOTE Confidence: 0.71403414

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

NOTE Confidence: 0.71403414

 $00{:}01{:}31{.}464 \dashrightarrow 00{:}01{:}33{.}650$ neurotransmitter in the brain with 80

NOTE Confidence: 0.71403414

 $00{:}01{:}33.650 \dashrightarrow 00{:}01{:}35.840$ to 90% of synapses being gluta matergic.

NOTE Confidence: 0.71403414

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

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

 $00:01:41.520 \rightarrow 00:01:43.260$ 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

 $00{:}01{:}45{.}000 \dashrightarrow 00{:}01{:}47{.}838$ 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

 $00{:}01{:}50{.}040 \dashrightarrow 00{:}01{:}52{.}240$ for fast excitatory transmission.

NOTE Confidence: 0.71403414

 $00:01:52.240 \longrightarrow 00:01:54.365$ Emmetabotropic have more of a

NOTE Confidence: 0.71403414

 $00{:}01{:}54.365 \dashrightarrow 00{:}01{:}57.063$ 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

 $00{:}01{:}59{.}920 \dashrightarrow 00{:}02{:}02{.}320$ It's AG protein coupled receptor.

NOTE Confidence: 0.71403414

 $00:02:02.320 \longrightarrow 00:02:04.255$ 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

 $00:02:05.803 \rightarrow 00:02:07.880$ brain and the peripheral tissue.

NOTE Confidence: 0.71403414

 $00:02:07.880 \longrightarrow 00:02:09.440$ It is involved in everything that

NOTE Confidence: 0.71403414

 $00:02:09.440 \rightarrow 00:02:10.900$ we do including learning, memory,

- NOTE Confidence: 0.71403414
- $00{:}02{:}10{.}900 \dashrightarrow 00{:}02{:}13{.}000$ anxiety and perception of pain.

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

NOTE Confidence: 0.71403414

 $00:02:16.048 \rightarrow 00:02:18.088$ allosteric modulation of the system

NOTE Confidence: 0.71403414

 $00:02:18.088 \rightarrow 00:02:19.720$ contributes to cognitive function,

NOTE Confidence: 0.71403414

 $00:02:19.720 \longrightarrow 00:02:20.334$ anxiety, pain.

NOTE Confidence: 0.71403414

 $00{:}02{:}20{.}334 \dashrightarrow 00{:}02{:}23{.}178$ A lot of this work has been done in

NOTE Confidence: 0.71403414

 $00{:}02{:}23.178 \dashrightarrow 00{:}02{:}25.418$ 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

 $00{:}02{:}27.760 \dashrightarrow 00{:}02{:}30.424$ And so the way I study Anglo 5 is

NOTE Confidence: 0.71403414

 $00:02:30.424 \rightarrow 00:02:33.360$ 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

 $00{:}02{:}36{.}304 \dashrightarrow 00{:}02{:}38{.}740$ what we actually study and how PET

NOTE Confidence: 0.71403414

 $00{:}02{:}38.740 \dashrightarrow 00{:}02{:}41.000$ 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

 $00:02:42.960 \longrightarrow 00:02:44.956$ the data that I will show you later.

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

NOTE Confidence: 0.71403414

 $00{:}02{:}46{.}560 \dashrightarrow 00{:}02{:}48{.}822$ which is a large machine that

NOTE Confidence: 0.71403414

 $00:02:48.822 \dashrightarrow 00:02:50.406$ makes radioactive particles such

NOTE Confidence: 0.71403414

 $00:02:50.406 \longrightarrow 00:02:52.636$ as carbon 11 and F18,

NOTE Confidence: 0.71403414

 $00{:}02{:}52{.}640 \dashrightarrow 00{:}02{:}55{.}624$ which we then bind to whatever target

NOTE Confidence: 0.71403414

 $00{:}02{:}55{.}624 \dashrightarrow 00{:}02{:}57{.}752$ you're sending into the brain to bind

NOTE Confidence: 0.71403414

 $00:02:57.752 \rightarrow 00:03:00.399$ to the enzyme neurotransmitter receptor,

NOTE Confidence: 0.71403414

 $00:03:00.400 \rightarrow 00:03:02.598$ 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

 $00{:}03{:}05{.}000 \dashrightarrow 00{:}03{:}06{.}640$ radio pharmaceutical or radio

NOTE Confidence: 0.71403414

 $00:03:06.640 \longrightarrow 00:03:08.320$ ligand or radio tracer.

NOTE Confidence: 0.71403414

 $00:03:08.320 \longrightarrow 00:03:11.000$ 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

 $00:03:12.835 \longrightarrow 00:03:14.670$ I'll say ligand or tracer

NOTE Confidence: 0.62159127

 $00:03:14.741 \longrightarrow 00:03:16.995$ and it all means the same thing.

NOTE Confidence: 0.62159127

 $00:03:17.000 \rightarrow 00:03:19.247$ We inject this into the subject as

 $00{:}03{:}19{.}247 \dashrightarrow 00{:}03{:}21{.}723$ a bolus over a one minute push or

NOTE Confidence: 0.62159127

 $00:03:21.723 \longrightarrow 00:03:23.421$ 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

 $00:03:25.379 \rightarrow 00:03:27.748$ on the system that we're studying.

NOTE Confidence: 0.62159127

 $00:03:27.748 \longrightarrow 00:03:29.833$ And then we acquire images.

NOTE Confidence: 0.62159127

 $00:03:29.840 \rightarrow 00:03:32.640$ 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

 $00:03:33.880 \longrightarrow 00:03:36.877$ 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

 $00{:}03{:}39{.}484 \dashrightarrow 00{:}03{:}41{.}860$ bore where only the subject's head

NOTE Confidence: 0.62159127

 $00:03:41.860 \dashrightarrow 00:03:44.315$ is positioned and so people with

NOTE Confidence: 0.62159127

 $00:03:44.315 \rightarrow 00:03:46.550$ 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

 $00{:}03{:}48{.}384 \dashrightarrow 00{:}03{:}50{.}114$ Now we have different scanners

NOTE Confidence: 0.62159127

 $00:03:50.114 \dashrightarrow 00:03:52.131$ with where the bore is larger and

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

NOTE Confidence: 0.62159127

 $00:03:53.760 \dashrightarrow 00:03:56.640$ So we do account for claustrophobia.

NOTE Confidence: 0.62159127

 $00:03:56.640 \longrightarrow 00:03:58.280$ And so as Jerry mentioned,

NOTE Confidence: 0.62159127

 $00:03:58.280 \rightarrow 00:04:01.600$ 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

 $00{:}04{:}06{.}512 \dashrightarrow 00{:}04{:}08{.}618$ And I'm really honoured to be able

NOTE Confidence: 0.62159127

 $00{:}04{:}08.618 \dashrightarrow 00{:}04{:}10.459$ 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

 $00:04:12.165 \longrightarrow 00:04:13.877$ I can ask people how do they feel,

NOTE Confidence: 0.62159127

 $00{:}04{:}13.880 \dashrightarrow 00{:}04{:}15.560$ 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

 $00{:}04{:}17{.}000 \dashrightarrow 00{:}04{:}21{.}480$ unite the human and neuroscience.

NOTE Confidence: 0.62159127

 $00:04:21.480 \longrightarrow 00:04:24.301$ And so this is an example of

NOTE Confidence: 0.62159127

 $00:04:24.301 \rightarrow 00:04:27.160$ 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

 $00:04:29.338 \rightarrow 00:04:31.237$ to guide placements of regions

NOTE Confidence: 0.62159127

 $00{:}04{:}31{.}237 \dashrightarrow 00{:}04{:}33{.}695$ of interest for PET and to make

NOTE Confidence: 0.62159127

 $00{:}04{:}33.695 \dashrightarrow 00{:}04{:}35.320$ sure there are no abnormalities.

NOTE Confidence: 0.62159127

 $00{:}04{:}35{.}320 \dashrightarrow 00{:}04{:}37{.}624$ 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

 $00:04:40.317 \longrightarrow 00:04:42.695$ that and then the radio chemist

NOTE Confidence: 0.62159127

 $00{:}04{:}42.695 \dashrightarrow 00{:}04{:}45.103$ synthesize the radio tracer when the

NOTE Confidence: 0.62159127

 $00{:}04{:}45{.}103 \dashrightarrow 00{:}04{:}47{.}315$ subjects show up at the PET scan.

NOTE Confidence: 0.62159127

 $00:04:47.320 \longrightarrow 00:04:48.657$ 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

 $00:04:49.640 \longrightarrow 00:04:53.000$ The radio tracers have a half

NOTE Confidence: 0.62159127

 $00{:}04{:}53{.}000 \dashrightarrow 00{:}04{:}54{.}360$ life of some 20 minutes,

NOTE Confidence: 0.62159127

 $00{:}04{:}54{.}360 \dashrightarrow 00{:}04{:}55{.}341$ some 110 minutes.

NOTE Confidence: 0.62159127

 $00{:}04{:}55{.}341 \dashrightarrow 00{:}04{:}57{.}630$ And so it's not something that can

NOTE Confidence: 0.62159127

 $00{:}04{:}57.697 \dashrightarrow 00{:}04{:}59.809$ be done in batches and distributed

 $00:04:59.809 \rightarrow 00:05:01.600$ throughout the day or week.

NOTE Confidence: 0.62159127

 $00{:}05{:}01{.}600 \dashrightarrow 00{:}05{:}04{.}183$ And then we collect bloods for metabolism

NOTE Confidence: 0.62159127

 $00:05:04.183 \rightarrow 00:05:06.558$ 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

 $00:05:08.200 \rightarrow 00:05:09.888$ their systems work differently.

NOTE Confidence: 0.62159127

 $00:05:09.888 \longrightarrow 00:05:12.420$ And then we inject the radio

NOTE Confidence: 0.62159127

 $00:05:12.490 \dashrightarrow 00:05:14.600$ tracer and collect PET images.

NOTE Confidence: 0.62159127

 $00:05:14.600 \longrightarrow 00:05:17.295$ And so this is an example of

NOTE Confidence: 0.62159127

 $00{:}05{:}17.295 \dashrightarrow 00{:}05{:}20.000$ a PET image and Amar image.

NOTE Confidence: 0.62159127

 $00:05:20.000 \rightarrow 00:05:23.320$ And so for pet outcome measures we have,

NOTE Confidence: 0.62159127

 $00:05:23.320 \longrightarrow 00:05:24.331$ we have several,

NOTE Confidence: 0.62159127

 $00:05:24.331 \longrightarrow 00:05:26.353$ but I'll be talking about two.

NOTE Confidence: 0.62159127

 $00:05:26.360 \rightarrow 00:05:29.440$ One is BPNT, which is a binding potential.

NOTE Confidence: 0.62159127

 $00:05:29.440 \dashrightarrow 00:05:31.414$ It's how much radioactivity we have in

NOTE Confidence: 0.62159127

 $00:05:31.414 \rightarrow 00:05:33.519$ a region that you're trying to study

NOTE Confidence: 0.62159127

 $00:05:33.520 \rightarrow 00:05:35.422$ versus how much radioactivity is in

 $00:05:35.422 \rightarrow 00:05:37.617$ the region that has nothing of what

NOTE Confidence: 0.62159127

 $00{:}05{:}37.617 \dashrightarrow 00{:}05{:}39.633$ it is that you're trying to study.

NOTE Confidence: 0.62159127

 $00:05:39.640 \rightarrow 00:05:42.436$ 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

 $00{:}05{:}43.812 \dashrightarrow 00{:}05{:}46.264$ we don't have that and so we

NOTE Confidence: 0.62159127

 $00{:}05{:}46.264 \dashrightarrow 00{:}05{:}47.560$ have to measure blood.

NOTE Confidence: 0.62159127

 $00{:}05{:}47{.}560 \dashrightarrow 00{:}05{:}49{.}814$ And so we look at how much

NOTE Confidence: 0.62159127

 $00{:}05{:}49{.}814 \dashrightarrow 00{:}05{:}52{.}220$ radioactivity is in the brain and the

NOTE Confidence: 0.62159127

 $00:05:52.220 \dashrightarrow 00:05:54.440$ tissue that you're trying to study

NOTE Confidence: 0.62159127

 $00:05:54.440 \dashrightarrow 00:05:56.718$ versus how much is in the blood.

NOTE Confidence: 0.62159127

 $00:05:56.720 \dashrightarrow 00:05:58.560$ And so the first one is called BPNT

NOTE Confidence: 0.62159127

 $00{:}05{:}58{.}560 \dashrightarrow 00{:}06{:}00{.}360$ and the second one is called BT.

NOTE Confidence: 0.62159127

 $00{:}06{:}00{.}360 \dashrightarrow 00{:}06{:}01{.}836$ And I as I go through,

NOTE Confidence: 0.62159127

 $00:06:01.840 \longrightarrow 00:06:03.200$ I will tell you which one I used.

NOTE Confidence: 0.5679808

 $00{:}06{:}05{.}240 \dashrightarrow 00{:}06{:}08{.}468$ We have two radio ligands that most

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

NOTE Confidence: 0.5679808

 $00{:}06{:}11.432 \dashrightarrow 00{:}06{:}14.520$ in vivo and I have used both of these.

NOTE Confidence: 0.5679808

 $00:06:14.520 \longrightarrow 00:06:17.224$ One is F18 FPEB, it has very high

NOTE Confidence: 0.5679808

 $00:06:17.224 \dashrightarrow 00:06:19.377$ affinity and specificity for the

NOTE Confidence: 0.5679808

 $00{:}06{:}19.377 \dashrightarrow 00{:}06{:}21.717$ receptor has slower kinetics of

NOTE Confidence: 0.5679808

 $00{:}06{:}21.720 \dashrightarrow 00{:}06{:}25.462$ 110 minute half life and that

NOTE Confidence: 0.5679808

 $00{:}06{:}25{.}462 \dashrightarrow 00{:}06{:}27{.}317$ sorry half life's 110 minutes.

NOTE Confidence: 0.5679808

 $00{:}06{:}27{.}320 \dashrightarrow 00{:}06{:}29{.}609$ And we think because of its high

NOTE Confidence: 0.5679808

 $00{:}06{:}29{.}609 \dashrightarrow 00{:}06{:}31{.}039$ specificity it's well suited

NOTE Confidence: 0.5679808

 $00:06:31.039 \dashrightarrow 00:06:32.959$ 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

 $00{:}06{:}36{.}370 \dashrightarrow 00{:}06{:}38{.}920$ 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

 $00{:}06{:}40.600 \dashrightarrow 00{:}06{:}42.840$ not as good as FBEB but because

NOTE Confidence: 0.5679808

 $00:06:42.840 \longrightarrow 00:06:44.920$ of its short half life we can do

- NOTE Confidence: 0.5679808
- $00:06:44.979 \longrightarrow 00:06:46.629$ challenge studies on the same

 $00{:}06{:}46.629 \dashrightarrow 00{:}06{:}48.701$ day we can administer this radio

NOTE Confidence: 0.5679808

 $00:06:48.701 \longrightarrow 00:06:50.117$ 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

 $00:06:52.960 \dashrightarrow 00:06:55.067$ which means they bind on the receptor

NOTE Confidence: 0.5679808

 $00:06:55.067 \rightarrow 00:06:58.347$ on a site different from where they're

NOTE Confidence: 0.5679808

 $00:06:58.347 \rightarrow 00:07:00.078$ endogenous neurotransmitter binds.

NOTE Confidence: 0.5679808

 $00:07:00.080 \longrightarrow 00:07:02.160$ 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

 $00:07:06.290 \longrightarrow 00:07:08.104$ what typically happens in the

NOTE Confidence: 0.56170344

 $00{:}07{:}08.104 \dashrightarrow 00{:}07{:}10.034$ 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

 $00:07:12.026 \longrightarrow 00:07:13.560$ what happens with Anglo 5.

NOTE Confidence: 0.56170344

 $00{:}07{:}13.560 \dashrightarrow 00{:}07{:}16.479$ So this was published by Mark Laurel,

NOTE Confidence: 0.56170344

 $00:07:16.480 \dashrightarrow 00:07:20.228$ who was a trainee here a few decades ago.

 $00:07:20.228 \dashrightarrow 00:07:23.118$ Then he was here again for a few months,

NOTE Confidence: 0.56170344

 $00{:}07{:}23.120 \dashrightarrow 00{:}07{:}25.493$ maybe a decade ago, and he explained

NOTE Confidence: 0.56170344

 $00{:}07{:}25{.}493 \dashrightarrow 00{:}07{:}28{.}280$ really well the classical occupancy model.

NOTE Confidence: 0.56170344

 $00:07:28.280 \longrightarrow 00:07:31.840$ 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

 $00{:}07{:}34.960 \dashrightarrow 00{:}07{:}38.600$ the the black triangles is dopamine,

NOTE Confidence: 0.56170344

 $00{:}07{:}38.600 \dashrightarrow 00{:}07{:}40.658$ the endogenous neurotransmitter

NOTE Confidence: 0.56170344

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

NOTE Confidence: 0.56170344

 $00{:}07{:}42.720 \dashrightarrow 00{:}07{:}45.156$ and the Pentagon shapes are rocklopride,

NOTE Confidence: 0.56170344

 $00{:}07{:}45.160 \dashrightarrow 00{:}07{:}46.456$ our radio tracer.

NOTE Confidence: 0.56170344

 $00{:}07{:}46.456 \dashrightarrow 00{:}07{:}48.616$ So in the typical situation

NOTE Confidence: 0.56170344

 $00{:}07{:}48.616 \dashrightarrow 00{:}07{:}50.559$ in the middle here,

NOTE Confidence: 0.56170344

 $00:07:50.560 \dashrightarrow 00:07:52.275$ some of the receptors are going to

NOTE Confidence: 0.56170344

 $00:07:52.275 \longrightarrow 00:07:54.178$ be occupied by dopamine, not all.

NOTE Confidence: 0.56170344

 $00{:}07{:}54.178 \dashrightarrow 00{:}07{:}56.152$ And so the radio ligand can

NOTE Confidence: 0.56170344

 $00:07:56.152 \rightarrow 00:07:58.000$ occupy the other receptors.

- NOTE Confidence: 0.56170344
- $00:07:58.000 \rightarrow 00:08:01.042$ So the endogenous neurotransmitter has higher

 $00:08:01.042 \rightarrow 00:08:04.124$ affinity or higher ligand for the receptor,

NOTE Confidence: 0.56170344

 $00:08:04.124 \longrightarrow 00:08:06.420$ so it's going to the radio

NOTE Confidence: 0.56170344

 $00:08:06.420 \rightarrow 00:08:08.320$ ligand cannot kick them off.

NOTE Confidence: 0.56170344

 $00{:}08{:}08{.}320 \dashrightarrow 00{:}08{:}09{.}950$ So whatever dopamine does not

NOTE Confidence: 0.56170344

 $00{:}08{:}09{.}950 \dashrightarrow 00{:}08{:}12{.}040$ occupy is what rectified can occupy.

NOTE Confidence: 0.56170344

 $00:08:12.040 \rightarrow 00:08:15.316$ And so this is called receptor availability.

NOTE Confidence: 0.56170344

 $00:08:15.320 \longrightarrow 00:08:17.078$ 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

 $00:08:19.616 \longrightarrow 00:08:20.720$ we gave subjects

NOTE Confidence: 0.67398137

 $00{:}08{:}22.800 \dashrightarrow 00{:}08{:}24.800$ a medication that induces dopamine

NOTE Confidence: 0.67398137

 $00{:}08{:}24.800 \dashrightarrow 00{:}08{:}27.544$ relief or a dopamine release or we have a

NOTE Confidence: 0.67398137

 $00{:}08{:}27{.}544 \dashrightarrow 00{:}08{:}29{.}718$ condition where there's too much dopamine,

NOTE Confidence: 0.67398137

 $00:08:29.720 \longrightarrow 00:08:31.664$ we don't have as many receptors

 $00:08:31.664 \rightarrow 00:08:33.440$ for the radioligand to occupy.

NOTE Confidence: 0.67398137

 $00:08:33.440 \longrightarrow 00:08:35.060$ So now we're measuring

NOTE Confidence: 0.67398137

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

NOTE Confidence: 0.67398137

 $00:08:36.280 \dashrightarrow 00:08:37.954$ And then on the left here is the opposite.

NOTE Confidence: 0.67398137

 $00:08:37.960 \dashrightarrow 00:08:39.468$ 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

 $00{:}08{:}45{.}554 \dashrightarrow 00{:}08{:}47{.}639$ we have more receptors available

NOTE Confidence: 0.67398137

 $00:08:47.639 \rightarrow 00:08:49.950$ and so high receptor availability

NOTE Confidence: 0.67398137

 $00:08:49.950 \longrightarrow 00:08:52.400$ 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

 $00:08:56.800 \dashrightarrow 00:09:00.552$ So the endogenous ligand glutamate is

NOTE Confidence: 0.67398137

 $00:09:00.552 \rightarrow 00:09:03.520$ going to bind in the extrasynaptic space,

NOTE Confidence: 0.67398137

 $00:09:03.520 \longrightarrow 00:09:05.950$ but the radioligand binds in

- NOTE Confidence: 0.67398137
- $00{:}09{:}05{.}950 \dashrightarrow 00{:}09{:}07{.}464$ the membrane space.
- NOTE Confidence: 0.67398137
- $00:09:07.464 \dashrightarrow 00:09:10.024$ So there's no direct competition
- NOTE Confidence: 0.67398137
- $00{:}09{:}10.024 \dashrightarrow 00{:}09{:}13.150$ between the endogenous ligand and the
- NOTE Confidence: 0.67398137
- $00:09:13.150 \longrightarrow 00:09:16.239$ neurotransmitter and the radio ligand.
- NOTE Confidence: 0.67398137
- $00:09:16.240 \dashrightarrow 00:09:19.474$ So whatever happens at the glutamate site
- NOTE Confidence: 0.67398137
- $00{:}09{:}19{.}480 \dashrightarrow 00{:}09{:}23{.}638$ may not influence the radio ligand site.
- NOTE Confidence: 0.67398137
- $00:09:23.640 \dashrightarrow 00:09:26.125$ And I was really trying hard to
- NOTE Confidence: 0.67398137
- $00{:}09{:}26.125 \dashrightarrow 00{:}09{:}28.249$ understand that concept and some other
- NOTE Confidence: 0.67398137
- $00:09:28.249 \dashrightarrow 00:09:30.552$ 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
- $00:09:39.594 \rightarrow 00:09:42.179$ 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

 $00{:}09{:}50{.}784 \dashrightarrow 00{:}09{:}53{.}536$ and he saw that it did not influence

NOTE Confidence: 0.67398137

 $00:09:53.536 \rightarrow 00:09:56.435$ the binding of the radioligand so again,

NOTE Confidence: 0.67398137

 $00:09:56.440 \longrightarrow 00:09:57.280$ as I showed you before,

NOTE Confidence: 0.67398137

 $00:09:57.280 \longrightarrow 00:09:58.932$ there's no drug competition

NOTE Confidence: 0.67398137

 $00:09:58.932 \dashrightarrow 00:10:02.772$ between ligand and glutamate.

NOTE Confidence: 0.67398137

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

NOTE Confidence: 0.67398137

 $00{:}10{:}04.280 \dashrightarrow 00{:}10{:}07.760$ when he administered an agonist,

NOTE Confidence: 0.67398137

 $00:10:07.760 \longrightarrow 00:10:08.432$ however, sorry,

NOTE Confidence: 0.67398137

 $00{:}10{:}08{.}432 \dashrightarrow 00{:}10{:}10{.}448$ he was trying to also measure

NOTE Confidence: 0.67398137

 $00:10:10.448 \longrightarrow 00:10:11.120$ internalized receptors.

NOTE Confidence: 0.67398137

 $00{:}10{:}11{.}120 \dashrightarrow 00{:}10{:}14{.}312$ And he could not measure internalized

NOTE Confidence: 0.67398137

 $00:10:14.312 \rightarrow 00:10:15.908$ receptors without administering

NOTE Confidence: 0.67398137

 $00{:}10{:}15{.}908 \dashrightarrow 00{:}10{:}18{.}310$ something that's going to permealize the

NOTE Confidence: 0.67398137

 $00{:}10{:}18{.}310 \dashrightarrow 00{:}10{:}21{.}075$ membrane and let the radio ligand in.

NOTE Confidence: 0.67398137

 $00:10:21.080 \rightarrow 00:10:24.257$ So here we see that the radio ligand cannot

NOTE Confidence: 0.67398137

 $00:10:24.257 \rightarrow 00:10:27.356$ cross the membrane and bind to Homer cells.

- NOTE Confidence: 0.67398137
- $00:10:27.360 \rightarrow 00:10:29.958$ But when they permealize the membrane,
- NOTE Confidence: 0.67398137
- $00{:}10{:}29{.}960 \dashrightarrow 00{:}10{:}33{.}166$ the radio ligand can bind and
- NOTE Confidence: 0.67398137
- $00:10:33.166 \longrightarrow 00:10:34.264$ 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
- $00:10:36.964 \rightarrow 00:10:39.487$ in red is just sending the
- NOTE Confidence: 0.67398137
- $00{:}10{:}39{.}487 \dashrightarrow 00{:}10{:}41{.}581$ radioligand in it cannot cross the
- NOTE Confidence: 0.67398137
- $00:10:41.581 \rightarrow 00:10:43.957$ and bind to internalized receptors.
- NOTE Confidence: 0.67398137
- $00{:}10{:}43.960 \dashrightarrow 00{:}10{:}46.256$ And in purple when we make little holes
- NOTE Confidence: 0.67398137
- $00:10:46.256 \longrightarrow 00:10:48.637$ in the membrane with the detergent,
- NOTE Confidence: 0.67398137
- $00:10:48.640 \longrightarrow 00:10:50.728$ it can cross the membrane and
- NOTE Confidence: 0.67398137
- $00{:}10{:}50.728 \dashrightarrow 00{:}10{:}52.120$ bind to internalized receptors.
- NOTE Confidence: 0.67398137
- $00{:}10{:}52.120 \dashrightarrow 00{:}10{:}54.766$ So this is really second really
- NOTE Confidence: 0.67398137
- $00:10:54.766 \rightarrow 00:10:57.153$ important concept that our radioligands
- NOTE Confidence: 0.67398137
- $00{:}10{:}57.153 \dashrightarrow 00{:}10{:}59.341$ cannot bind to internalized
- NOTE Confidence: 0.67398137
- $00:10:59.341 \longrightarrow 00:11:02.076$ receptors unless they get help.
- NOTE Confidence: 0.67398137

- $00:11:02.080 \longrightarrow 00:11:04.096$ And so I was really excited to see that
- NOTE Confidence: 0.67398137
- $00:11:04.096 \rightarrow 00:11:06.036$ 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
- $00:11:06.415 \rightarrow 00:11:08.665$ 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
- $00:11:11.848 \longrightarrow 00:11:12.272$ 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
- $00:11:16.844 \dashrightarrow 00:11:18.540$ cannot pass through the membrane.
- NOTE Confidence: 0.67398137
- $00{:}11{:}18{.}540 \dashrightarrow 00{:}11{:}21{.}400$ So I went back to Jonathan and he showed you.
- NOTE Confidence: 0.67398137
- $00:11:21.400 \rightarrow 00:11:23.596$ So this is what I just showed you before.
- NOTE Confidence: 0.67398137
- $00{:}11{:}23.600 \dashrightarrow 00{:}11{:}28.478$ He showed that the radioligand these
- NOTE Confidence: 0.67398137
- $00:11:28.480 \longrightarrow 00:11:30.904$ 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
- $00:11:35.344 \rightarrow 00:11:37.238$ 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
- $00:11:39.022 \longrightarrow 00:11:41.048$ because a lot of the other
- NOTE Confidence: 0.67398137
- $00:11:41.048 \rightarrow 00:11:43.364$ ligands that we study can actually
- NOTE Confidence: 0.67398137
- $00:11:43.364 \rightarrow 00:11:44.800$ measure internalized receptors.
- NOTE Confidence: 0.67398137
- $00{:}11{:}44{.}800 \dashrightarrow 00{:}11{:}46{.}774$ And so the explanation of what
- NOTE Confidence: 0.67398137
- $00:11:46.774 \longrightarrow 00:11:48.090$ it is that we're
- NOTE Confidence: 0.55249465
- $00:11:48.160 \longrightarrow 00:11:50.398$ seeing is going to be different.
- NOTE Confidence: 0.55249465
- $00:11:50.400 \longrightarrow 00:11:52.638$ 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
- $00:11:59.645 \rightarrow 00:12:01.864$ this first study and then she did
- NOTE Confidence: 0.55249465
- $00:12:01.864 \longrightarrow 00:12:03.676$ the second study here at Yale.
- NOTE Confidence: 0.55249465
- $00:12:03.680 \rightarrow 00:12:06.680$ So when we bring up new radio ligands,
- NOTE Confidence: 0.55249465

 $00:12:06.680 \rightarrow 00:12:08.985$ we go through different processes

NOTE Confidence: 0.55249465

 $00:12:08.985 \longrightarrow 00:12:11.807$ of studying them in cells and

NOTE Confidence: 0.55249465

 $00:12:11.807 \longrightarrow 00:12:13.957$ 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

 $00{:}12{:}15{.}920 \dashrightarrow 00{:}12{:}17{.}536$ we need to do test, retest studies.

NOTE Confidence: 0.55249465

 $00:12:17.536 \rightarrow 00:12:20.320$ So we administer the ligand in the morning,

NOTE Confidence: 0.55249465

 $00:12:20.320 \longrightarrow 00:12:22.448$ then we give the subjects a break

NOTE Confidence: 0.55249465

 $00{:}12{:}22{.}448 \dashrightarrow 00{:}12{:}24{.}012$ and minister in the afternoon

NOTE Confidence: 0.55249465

 $00{:}12{:}24.012 \dashrightarrow 00{:}12{:}26.348$ and we want to make sure that the

NOTE Confidence: 0.55249465

 $00:12:26.411 \longrightarrow 00:12:28.399$ 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

 $00{:}12{:}31.080 \dashrightarrow 00{:}12{:}32.480$ whatever it is you're trying to measure,

NOTE Confidence: 0.55249465

 $00:12:32.480 \rightarrow 00:12:34.600$ it is the same thing that you're measuring,

NOTE Confidence: 0.55249465

 $00:12:34.600 \rightarrow 00:12:37.558$ that there are no significant differences.

NOTE Confidence: 0.55249465

 $00:12:37.560 \longrightarrow 00:12:38.760$ And so back in the day,

NOTE Confidence: 0.55249465

 $00:12:38.760 \rightarrow 00:12:40.385$ these studies were done only

- NOTE Confidence: 0.55249465
- $00{:}12{:}40{.}385 \dashrightarrow 00{:}12{:}41{.}360$ in male subjects.
- NOTE Confidence: 0.55249465
- $00:12:41.360 \rightarrow 00:12:44.000$ 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
- $00:12:47.320 \rightarrow 00:12:51.192$ and contrary to the 1015 plus minus
- NOTE Confidence: 0.55249465
- $00:12:51.192 \longrightarrow 00:12:53.600$ test 3 test that we typically see,
- NOTE Confidence: 0.55249465
- $00:12:53.600 \longrightarrow 00:12:57.048$ Chrissy showed about 20 to 40% plus.
- NOTE Confidence: 0.55249465
- $00:12:57.048 \rightarrow 00:12:59.320$ So in the morning,
- NOTE Confidence: 0.55249465
- $00:12:59.320 \longrightarrow 00:13:01.870$ subjects were scanned and then their
- NOTE Confidence: 0.55249465
- $00:13:01.870 \longrightarrow 00:13:03.570$ receptor availabilities appeared to
- NOTE Confidence: 0.55249465
- $00:13:03.633 \longrightarrow 00:13:05.757$ go up in the afternoon by 20 to 40%.
- NOTE Confidence: 0.55249465
- $00{:}13{:}05{.}760 \dashrightarrow 00{:}13{:}08{.}118$ And so this was really puzzling.
- NOTE Confidence: 0.55249465
- $00{:}13{:}08{.}120 \dashrightarrow 00{:}13{:}09{.}436$ 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
- $00{:}13{:}12{.}720 \dashrightarrow 00{:}13{:}14{.}351$ so they're anxious in the morning and
- NOTE Confidence: 0.55249465

 $00:13:14.351 \rightarrow 00:13:16.676$ then in the afternoon they're not so anxious.

NOTE Confidence: 0.55249465

 $00:13:16.680 \longrightarrow 00:13:18.320$ Or was there something else?

NOTE Confidence: 0.55249465

 $00:13:18.320 \rightarrow 00:13:20.120$ Was there heart rate, you know,

NOTE Confidence: 0.55249465

 $00{:}13{:}20{.}120 \dashrightarrow 00{:}13{:}21{.}476$ 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

 $00:13:23.400 \longrightarrow 00:13:24.640$ And in the meantime,

NOTE Confidence: 0.55249465

 $00:13:24.640 \longrightarrow 00:13:26.660$ we all thought this was AVP 688.

NOTE Confidence: 0.55249465

 $00:13:26.660 \rightarrow 00:13:28.040$ 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

 $00:13:30.147 \rightarrow 00:13:32.398$ 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

 $00{:}13{:}33{.}740 \dashrightarrow 00{:}13{:}35{.}080$ and she did test,

NOTE Confidence: 0.55249465

 $00:13:35.080 \longrightarrow 00:13:36.102$ retest again,

NOTE Confidence: 0.55249465

 $00{:}13{:}36{.}102 \dashrightarrow 00{:}13{:}39{.}168$ 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
- $00{:}13{:}43.801 \dashrightarrow 00{:}13{:}46.206$ 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
- $00{:}13{:}52{.}275 \dashrightarrow 00{:}13{:}54{.}250$ increases in the afternoon scan
- NOTE Confidence: 0.55249465
- $00{:}13{:}54{.}250 \dashrightarrow 00{:}13{:}56{.}520$ 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
- $00:13:59.080 \longrightarrow 00:14:00.900$ so the females are in red and
- NOTE Confidence: 0.55249465
- $00{:}14{:}00{.}900 \dashrightarrow 00{:}14{:}02{.}320$ the males are in blue.
- NOTE Confidence: 0.55249465
- $00{:}14{:}02{.}320 \dashrightarrow 00{:}14{:}05{.}820$ Females showed a greater increase in the
- NOTE Confidence: 0.55249465
- $00:14:05.820 \longrightarrow 00:14:08.959$ 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
- $00:14:10.440 \longrightarrow 00:14:11.172$ reading literature.
- NOTE Confidence: 0.55249465
- $00:14:11.172 \rightarrow 00:14:13.368$ We also took people's heart rates
- NOTE Confidence: 0.55249465
- $00{:}14{:}13.368 \dashrightarrow 00{:}14{:}15.310$ and blood pressure and their
- NOTE Confidence: 0.55249465
- $00{:}14{:}15{.}310 \dashrightarrow 00{:}14{:}16{.}826$ anxiety levels etcetera, etcetera.
- NOTE Confidence: 0.55249465

 $00:14:16.826 \rightarrow 00:14:19.437$ 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

 $00:14:22.950 \rightarrow 00:14:25.560$ receptor availability over a few hours.

NOTE Confidence: 0.55249465

 $00:14:25.560 \rightarrow 00:14:27.876$ And we read some animal work,

NOTE Confidence: 0.55249465

 $00:14:27.880 \longrightarrow 00:14:29.384$ some medication development work.

NOTE Confidence: 0.55249465

 $00{:}14{:}29{.}384 \dashrightarrow 00{:}14{:}32{.}050$ And what became apparent to us was NOTE Confidence: 0.55249465

 $00:14:32.050 \rightarrow 00:14:34.114$ that we weren't studying test retest.

NOTE Confidence: 0.55249465

 $00:14:34.120 \rightarrow 00:14:36.598$ We were studying during our variation.

NOTE Confidence: 0.55249465

 $00{:}14{:}36{.}600 \dashrightarrow 00{:}14{:}38{.}736$ So for those of you who are not

NOTE Confidence: 0.55249465

 $00:14:38.736 \rightarrow 00:14:40.520$ 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

 $00{:}14{:}43{.}400 \dashrightarrow 00{:}14{:}45{.}178$ overnight and in the morning we wake NOTE Confidence: 0.55249465

 $00:14:45.178 \rightarrow 00:14:47.158$ 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

 $00{:}14{:}48.826 \dashrightarrow 00{:}14{:}50.638$ maybe a little chocolate or caffeine,

NOTE Confidence: 0.3123216

 $00:14:50.640 \rightarrow 00:14:52.544$ but you know, we're ready to start

- NOTE Confidence: 0.3123216
- $00:14:52.544 \rightarrow 00:14:55.040$ the day and get to work and do stuff.

 $00{:}14{:}55{.}040 \dashrightarrow 00{:}14{:}58{.}510$ And then over the afternoon our corisol

NOTE Confidence: 0.3123216

 $00:14:58.510 \rightarrow 00:15:00.995$ levels decrease and we get more tired,

NOTE Confidence: 0.3123216

 $00:15:01.000 \longrightarrow 00:15:02.328$ a bit more lethargic.

NOTE Confidence: 0.3123216

 $00:15:02.328 \rightarrow 00:15:05.112$ We're kind of done with the day and by

NOTE Confidence: 0.3123216

 $00:15:05.112 \longrightarrow 00:15:06.648$ evening they're the lowest and that's

NOTE Confidence: 0.3123216

 $00:15:06.648 \rightarrow 00:15:08.439$ when we are ready to go to sleep.

NOTE Confidence: 0.3123216

 $00:15:08.440 \longrightarrow 00:15:10.240$ And then the cycle continues.

NOTE Confidence: 0.3123216

 $00:15:10.240 \longrightarrow 00:15:12.440$ Well, animal literature shows that

NOTE Confidence: 0.3123216

 $00:15:12.440 \longrightarrow 00:15:14.222$ 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

 $00{:}15{:}20{.}000 \dashrightarrow 00{:}15{:}22{.}846$ So what we think is happening in our

NOTE Confidence: 0.3123216

 $00{:}15{:}22{.}846 \dashrightarrow 00{:}15{:}25{.}247$ test retest scanning is that in the

NOTE Confidence: 0.3123216

 $00{:}15{:}25{.}247 \dashrightarrow 00{:}15{:}27{.}716$ morning when Corso levels are highest,

 $00:15:27.720 \rightarrow 00:15:30.318$ we're observing lower Anglo 5 availability.

NOTE Confidence: 0.3123216

 $00{:}15{:}30{.}320 \dashrightarrow 00{:}15{:}32{.}952$ In the afternoon when the Corso levels

NOTE Confidence: 0.3123216

 $00{:}15{:}32{.}952 \dashrightarrow 00{:}15{:}35{.}895$ 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

 $00{:}15{:}38{.}320 \dashrightarrow 00{:}15{:}40{.}742$ 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

 $00:15:43.832 \longrightarrow 00:15:45.680$ measuring journal variation which

NOTE Confidence: 0.3123216

 $00:15:45.680 \rightarrow 00:15:47.120$ actually was something interesting.

NOTE Confidence: 0.3123216

 $00{:}15{:}47{.}120 \dashrightarrow 00{:}15{:}48{.}080$ And based on these data,

NOTE Confidence: 0.3123216

 $00{:}15{:}48.080 \dashrightarrow 00{:}15{:}51.328$ Chrissy got an RO one to study circadian

NOTE Confidence: 0.3123216

 $00{:}15{:}51{.}328 \dashrightarrow 00{:}15{:}54{.}253$ rhythm and sleep wake cycle in people

NOTE Confidence: 0.3123216

 $00{:}15{:}54{.}253 \dashrightarrow 00{:}15{:}57{.}639$ who are controls and who have depression.

NOTE Confidence: 0.3123216

 $00{:}15{:}57{.}640 \dashrightarrow 00{:}15{:}59{.}978$ 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

 $00:16:08.040 \rightarrow 00:16:11.619$ So this was maybe in 2008 or 2010

 $00:16:11.619 \rightarrow 00:16:14.370$ 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

 $00:16:19.692 \rightarrow 00:16:21.837$ important to our daily functioning.

NOTE Confidence: 0.41547155

 $00{:}16{:}21{.}840 \dashrightarrow 00{:}16{:}24{.}288$ 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

 $00{:}16{:}26.689 \dashrightarrow 00{:}16{:}28.834$ agents for treatment of depression.

NOTE Confidence: 0.41547155

 $00:16:28.840 \rightarrow 00:16:30.954$ But there was no work in human,

NOTE Confidence: 0.41547155

 $00{:}16{:}30{.}960 \dashrightarrow 00{:}16{:}33{.}640$ a lot of the work was done in animal studies.

NOTE Confidence: 0.41547155

 $00:16:33.640 \rightarrow 00:16:36.484$ And so we thought that it would be good

NOTE Confidence: 0.41547155

 $00{:}16{:}36{.}484 \dashrightarrow 00{:}16{:}39{.}304$ to to invivo human work and see if Mglu

NOTE Confidence: 0.41547155

 $00{:}16{:}39{.}304 \dashrightarrow 00{:}16{:}41{.}344$ 5 actually plays a role in depression.

NOTE Confidence: 0.41547155

 $00{:}16{:}41{.}344 \dashrightarrow 00{:}16{:}44{.}199$ 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

 $00{:}16{:}46{.}240 \dashrightarrow 00{:}16{:}48{.}400$ There was a preliminary study published

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

NOTE Confidence: 0.41547155

 $00{:}16{:}50{.}574 \dashrightarrow 00{:}16{:}52{.}776$ 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

 $00{:}17{:}03.189 \dashrightarrow 00{:}17{:}06.280$ group associated with anxiety symptoms.

NOTE Confidence: 0.41547155

 $00{:}17{:}06{.}280 \dashrightarrow 00{:}17{:}08{.}653$ And so I had the opportunity to

NOTE Confidence: 0.41547155

 $00:17:08.653 \rightarrow 00:17:11.520$ 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

 $00:17:15.240 \rightarrow 00:17:18.240$ which for PET is quite a large study.

NOTE Confidence: 0.41547155

 $00{:}17{:}18.240 \dashrightarrow 00{:}17{:}20.640$ They were all unmedicated 35 years

NOTE Confidence: 0.41547155

 $00:17:20.640 \rightarrow 00:17:22.240$ of age on average.

NOTE Confidence: 0.41547155

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

NOTE Confidence: 0.41547155

 $00:17:23.976 \longrightarrow 00:17:25.278$ measured with PDI,

NOTE Confidence: 0.41547155

 $00{:}17{:}25{.}280 \dashrightarrow 00{:}17{:}28{.}520$ modulus and AMD and then we had 35

NOTE Confidence: 0.41547155

 $00:17:28.520 \rightarrow 00:17:31.318$ healthy controls who were matched by sex,

- NOTE Confidence: 0.41547155
- $00:17:31.320 \longrightarrow 00:17:33.420$ age and smoking status.

 $00:17:33.420 \longrightarrow 00:17:36.650$ 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

 $00:17:39.475 \rightarrow 00:17:41.800$ 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

 $00{:}17{:}45{.}560 \dashrightarrow 00{:}17{:}46{.}840$ and Mrs.

NOTE Confidence: 0.41547155

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

NOTE Confidence: 0.41547155

 $00:17:49.120 \longrightarrow 00:17:51.848$ This part of the study was done in

NOTE Confidence: 0.41547155

 $00{:}17{:}51{.}848 \dashrightarrow 00{:}17{:}53{.}440$ collaboration with Graham Mason.

NOTE Confidence: 0.41547155

 $00{:}17{:}53{.}440 \dashrightarrow 00{:}17{:}55{.}743$ We use a magnet to study metabolic

NOTE Confidence: 0.41547155

 $00{:}17{:}55{.}743 \dashrightarrow 00{:}17{:}57{.}200$ changes in the brain.

NOTE Confidence: 0.41547155

 $00{:}17{:}57{.}200 \dashrightarrow 00{:}17{:}59{.}006$ All the measurements are in tissue

NOTE Confidence: 0.41547155

 $00:17:59.006 \rightarrow 00:18:01.040$ and when when we get the data,

NOTE Confidence: 0.41547155

 $00:18:01.040 \rightarrow 00:18:03.384$ it's put into a spectrum and each metabolite

 $00:18:03.384 \rightarrow 00:18:05.440$ has its own peak in the spectrum.

NOTE Confidence: 0.41547155

 $00{:}18{:}05{.}440 \dashrightarrow 00{:}18{:}07{.}841$ And so this was back back in

NOTE Confidence: 0.41547155

 $00:18:07.841 \rightarrow 00:18:10.489$ the day when we couldn't really

NOTE Confidence: 0.41547155

 $00:18:10.489 \rightarrow 00:18:13.555$ separate glutamate and GLN too well.

NOTE Confidence: 0.41547155

 $00:18:13.560 \longrightarrow 00:18:14.644$ So we studied GLX,

NOTE Confidence: 0.41547155

 $00:18:14.644 \rightarrow 00:18:17.119$ which is the sum of glutamate and glutamine.

NOTE Confidence: 0.8321714

 $00{:}18{:}19{.}520 \dashrightarrow 00{:}18{:}22{.}700$ And the other caveat with Mrs. is that,

NOTE Confidence: 0.8321714

 $00:18:22.700 \rightarrow 00:18:25.280$ especially when I started doing this,

NOTE Confidence: 0.8321714

 $00{:}18{:}25{.}280 \dashrightarrow 00{:}18{:}27{.}760$ we could only do one voxel at a time because

NOTE Confidence: 0.8321714

 $00{:}18{:}27{.}821 \dashrightarrow 00{:}18{:}30{.}071$ it took us about two hours to do 1 scan.

NOTE Confidence: 0.8321714

 $00{:}18{:}30{.}080 \dashrightarrow 00{:}18{:}31{.}694$ And as you can imagine, the subjects

NOTE Confidence: 0.8321714

 $00{:}18{:}31.694 \dashrightarrow 00{:}18{:}33.510$ were not going to be in the scanner

NOTE Confidence: 0.8321714

 $00:18:33.560 \longrightarrow 00:18:35.360$ for four hours for us to get 2 voxels.

NOTE Confidence: 0.8321714

 $00:18:35.360 \longrightarrow 00:18:37.705$ And so we decided to study the

NOTE Confidence: 0.8321714

 $00:18:37.705 \rightarrow 00:18:39.313$ anterior singular cortex given its

NOTE Confidence: 0.8321714

 $00:18:39.313 \rightarrow 00:18:43.438$ role in mood and cognitive processes.

 $00{:}18{:}43{.}440 \dashrightarrow 00{:}18{:}45{.}960$ And so this is our main outcome.

NOTE Confidence: 0.8321714

 $00{:}18{:}45{.}960 \dashrightarrow 00{:}18{:}48{.}193$ So the healthy controls are in diamonds

NOTE Confidence: 0.8321714

 $00:18:48.193 \rightarrow 00:18:50.510$ and people with depression are in circles.

NOTE Confidence: 0.8321714

 $00:18:50.510 \rightarrow 00:18:52.990$ We did not see any differences between groups

NOTE Confidence: 0.8321714

 $00:18:52.990 \rightarrow 00:18:55.319$ 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

 $00:18:57.528 \rightarrow 00:19:00.104$ the whole brain and we saw nothing

NOTE Confidence: 0.8321714

 $00{:}19{:}00{.}104 \dashrightarrow 00{:}19{:}01{.}759$ across the whole brain.

NOTE Confidence: 0.8321714

 $00:19:01.760 \longrightarrow 00:19:05.600$ The previous study used a reference

NOTE Confidence: 0.8321714

 $00:19:05.600 \longrightarrow 00:19:07.700$ region to calculate their outcomes.

NOTE Confidence: 0.8321714

 $00:19:07.700 \longrightarrow 00:19:09.525$ So even though Anglo fives

NOTE Confidence: 0.8321714

 $00{:}19{:}09{.}525 \dashrightarrow 00{:}19{:}11{.}438$ 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

 $00{:}19{:}16.420 \dashrightarrow 00{:}19{:}18.870$ why would it not see significant findings.

 $00:19:18.870 \longrightarrow 00:19:21.600$ 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

 $00:19:23.600 \rightarrow 00:19:26.477$ we did not see difference between groups.

NOTE Confidence: 0.8321714

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

NOTE Confidence: 0.8321714

 $00{:}19{:}26.716 \dashrightarrow 00{:}19{:}28.840$ if you go back and look at the literature,

NOTE Confidence: 0.8321714

 $00:19:28.840 \longrightarrow 00:19:31.120$ 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

 $00{:}19{:}33.010 \dashrightarrow 00{:}19{:}34.522$ showing no differences between

NOTE Confidence: 0.8321714

 $00{:}19{:}34{.}522 \dashrightarrow 00{:}19{:}36{.}439$ controls and people with depression,

NOTE Confidence: 0.8321714

 $00{:}19{:}36{.}440 \dashrightarrow 00{:}19{:}38{.}800$ with psychosis or no psychosis,

NOTE Confidence: 0.8321714

 $00:19:38.800 \longrightarrow 00:19:40.105$ and amplified availability.

NOTE Confidence: 0.8321714

 $00{:}19{:}40{.}105 \dashrightarrow 00{:}19{:}43{.}191$ And then we did our own autobadiography

NOTE Confidence: 0.8321714

 $00{:}19{:}43{.}191 \dashrightarrow 00{:}19{:}46{.}017$ study was showing no differences between

NOTE Confidence: 0.8321714

 $00:19:46.017 \rightarrow 00:19:48.211$ 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

 $00:19:50.360 \longrightarrow 00:19:52.640$ although there's a little more

 $00:19:52.640 \longrightarrow 00:19:54.920$ variability in the MDT group.

NOTE Confidence: 0.8321714

 $00:19:54.920 \rightarrow 00:19:58.720$ The novel part is that we of course did Mrs.

NOTE Confidence: 0.8321714

 $00:19:58.720 \rightarrow 00:20:03.680$ with PET and so we saw higher glutamate,

NOTE Confidence: 0.8321714

 $00{:}20{:}03.680 \dashrightarrow 00{:}20{:}05.870$ glutamine and GLX levels in people

NOTE Confidence: 0.8321714

 $00{:}20{:}05{.}870 \dashrightarrow 00{:}20{:}07{.}716$ with depression as compared to

NOTE Confidence: 0.8321714

 $00{:}20{:}07{.}716 \dashrightarrow 00{:}20{:}10{.}080$ controls and when we looked at

NOTE Confidence: 0.8321714

 $00:20:10.080 \rightarrow 00:20:12.411$ relationship between glutamate.

NOTE Confidence: 0.8321714

 $00{:}20{:}12{.}411 \dashrightarrow 00{:}20{:}17{.}073$ Or G glutamine or GLX and

NOTE Confidence: 0.8321714

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

NOTE Confidence: 0.8321714

 $00:20:17.944 \longrightarrow 00:20:20.536$ 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

 $00:20:21.920 \longrightarrow 00:20:24.758$ et cetera had low receptor availability.

NOTE Confidence: 0.8321714

 $00:20:24.760 \longrightarrow 00:20:26.956$ 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

 $00{:}20{:}29{.}438 \dashrightarrow 00{:}20{:}32{.}914$ would down regulate receptors which

 $00:20:32.914 \longrightarrow 00:20:35.399$ would then in turn internalize.

NOTE Confidence: 0.8321714

 $00{:}20{:}35{.}400 \dashrightarrow 00{:}20{:}36{.}966$ But this has never been shown

NOTE Confidence: 0.8321714

 $00:20:36.966 \longrightarrow 00:20:38.360$ in human in the vivo.

NOTE Confidence: 0.8321714

 $00:20:38.360 \rightarrow 00:20:41.360$ We've hypothesized for years that

NOTE Confidence: 0.8321714

 $00{:}20{:}41.360 \dashrightarrow 00{:}20{:}42.800$ too much glutamate is excited,

NOTE Confidence: 0.8321714

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

NOTE Confidence: 0.8321714

 $00{:}20{:}43.036 \dashrightarrow 00{:}20{:}44.452$ but that's the first time we

NOTE Confidence: 0.8321714

 $00:20:44.452 \rightarrow 00:20:46.000$ were able to show it in vivo,

NOTE Confidence: 0.8321714

 $00{:}20{:}46.000 \dashrightarrow 00{:}20{:}48.560$ and this was really exciting.

NOTE Confidence: 0.8321714

 $00{:}20{:}48.560 \dashrightarrow 00{:}20{:}54.370$ So this work has been published and

NOTE Confidence: 0.8321714

 $00{:}20{:}54.370 \dashrightarrow 00{:}20{:}57.172$ 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

 $00{:}20{:}58.800 \dashrightarrow 00{:}21{:}00.998$ 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

 $00{:}21{:}04{.}164 \dashrightarrow 00{:}21{:}08{.}304$ 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
- $00:21:10.241 \rightarrow 00:21:12.596$ disorder versus in unipolar disorder.

 $00{:}21{:}12.596 \dashrightarrow 00{:}21{:}15.230$ And this work was done in

NOTE Confidence: 0.8321714

 $00:21:15.313 \rightarrow 00:21:18.157$ collaboration with Hilary Blumberg.

NOTE Confidence: 0.8321714

 $00:21:18.160 \rightarrow 00:21:20.720$ And so we recruited people who are controls,

NOTE Confidence: 0.8321714

 $00:21:20.720 \rightarrow 00:21:22.960$ people who have bipolar depression,

NOTE Confidence: 0.8321714

 $00:21:22.960 \rightarrow 00:21:25.160$ people who have bipolar euthymia,

NOTE Confidence: 0.8321714

 $00:21:25.160 \rightarrow 00:21:27.757$ and then people who have unipolar depression.

NOTE Confidence: 0.8321714

 $00:21:27.760 \longrightarrow 00:21:30.120$ And although the grant did

NOTE Confidence: 0.8321714

 $00{:}21{:}30{.}120 \dashrightarrow 00{:}21{:}32{.}480$ not call for bipolar Euthymia,

NOTE Confidence: 0.8321714

 $00:21:32.480 \longrightarrow 00:21:34.400$ but when we recruited people and

NOTE Confidence: 0.8321714

 $00:21:34.400 \longrightarrow 00:21:36.297$ we did their screening and then

NOTE Confidence: 0.8321714

 $00{:}21{:}36{.}297 \dashrightarrow 00{:}21{:}37{.}953$ they showed up for PET scans,

NOTE Confidence: 0.28242582

 $00:21:37.960 \longrightarrow 00:21:39.880$ 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

 $00{:}21{:}42{.}424 \dashrightarrow 00{:}21{:}45{.}179$ with bipolar disorder cycle quite a bit.

 $00:21:45.179 \rightarrow 00:21:48.146$ So we amended our protocol and let people

NOTE Confidence: 0.28242582

 $00:21:48.146 \rightarrow 00:21:52.758$ with any mood state participate in the study.

NOTE Confidence: 0.28242582

 $00:21:52.760 \longrightarrow 00:21:54.160$ 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

 $00{:}21{:}57.800 \dashrightarrow 00{:}22{:}00{.}320$ except for depression status.

NOTE Confidence: 0.28242582

 $00{:}22{:}00{.}320 \dashrightarrow 00{:}22{:}02{.}324$ So people with bipolar disorder who

NOTE Confidence: 0.28242582

 $00:22:02.324 \rightarrow 00:22:04.068$ are depressed and unipolar disorder

NOTE Confidence: 0.28242582

 $00{:}22{:}04.068 \dashrightarrow 00{:}22{:}05.870$ who are depressed or more significantly

NOTE Confidence: 0.28242582

 $00:22:05.870 \rightarrow 00:22:07.120$ depressed than any other group,

NOTE Confidence: 0.28242582

 $00{:}22{:}07{.}120 \dashrightarrow 00{:}22{:}10.840$ another group was depressed.

NOTE Confidence: 0.28242582

 $00:22:10.840 \longrightarrow 00:22:13.108$ And so these are our data that

NOTE Confidence: 0.28242582

 $00{:}22{:}13.108 \dashrightarrow 00{:}22{:}14.936$ 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

 $00{:}22{:}17.080 \dashrightarrow 00{:}22{:}18.960$ the writing of the manuscript.

NOTE Confidence: 0.28242582

 $00:22:18.960 \longrightarrow 00:22:21.473$ And so we see that people who

- NOTE Confidence: 0.28242582
- $00{:}22{:}21{.}473 \dashrightarrow 00{:}22{:}23{.}000$ are controls aren't grey,
- NOTE Confidence: 0.28242582
- $00:22:23.000 \rightarrow 00:22:24.680$ people with unipolar depression
- NOTE Confidence: 0.28242582
- $00:22:24.680 \rightarrow 00:22:25.520$ aren't orange.
- NOTE Confidence: 0.28242582
- $00{:}22{:}25{.}520 \dashrightarrow 00{:}22{:}25{.}912$ Again,
- NOTE Confidence: 0.28242582
- $00{:}22{:}25{.}912 \dashrightarrow 00{:}22{:}27{.}480$ there's no difference receptor
- NOTE Confidence: 0.28242582
- $00:22:27.480 \longrightarrow 00:22:29.048$ availability between these two
- NOTE Confidence: 0.28242582
- $00:22:29.048 \rightarrow 00:22:31.360$ groups as we showed previously.
- NOTE Confidence: 0.28242582
- $00:22:31.360 \longrightarrow 00:22:33.760$ And then people bipolar disorder
- NOTE Confidence: 0.28242582
- $00:22:33.760 \rightarrow 00:22:36.371$ who are depressed or in purple and
- NOTE Confidence: 0.28242582
- $00{:}22{:}36{.}371 \dashrightarrow 00{:}22{:}39{.}557$ who are euthymic are in turquoise
- NOTE Confidence: 0.28242582
- $00:22:39.560 \rightarrow 00:22:41.639$ and both of these groups are lower
- NOTE Confidence: 0.28242582
- $00:22:41.639 \longrightarrow 00:22:42.973$ in their receptor availability
- NOTE Confidence: 0.28242582
- $00{:}22{:}42.973 \dashrightarrow 00{:}22{:}45.666$ as compared to controls and are
- NOTE Confidence: 0.28242582
- $00{:}22{:}45.666 \dashrightarrow 00{:}22{:}47.238$ unipolar depressed.
- NOTE Confidence: 0.28242582
- $00{:}22{:}47.240 \dashrightarrow 00{:}22{:}49.118$ And this was across brain regions.
- NOTE Confidence: 0.28242582

 $00:22:49.120 \rightarrow 00:22:50.720$ The prefrontal cortical regions

NOTE Confidence: 0.28242582

 $00:22:50.720 \longrightarrow 00:22:52.445$ were my main hypothesis,

NOTE Confidence: 0.28242582

 $00{:}22{:}52{.}445 \dashrightarrow 00{:}22{:}56{.}220$ but this was across the brain and NOTE Confidence: 0.28242582

 $00:22:56.220 \rightarrow 00:22:59.940$ what was really interesting as well

NOTE Confidence: 0.28242582

 $00{:}22{:}59{.}940 \dashrightarrow 00{:}23{:}02{.}756$ 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

 $00{:}23{:}06{.}200 \dashrightarrow 00{:}23{:}09{.}853$ 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

 $00{:}23{:}16{.}717 \dashrightarrow 00{:}23{:}19{.}120$ potentially to differentiate to disorders, NOTE Confidence: 0.28242582

 $00:23:19.120 \rightarrow 00:23:22.288$ but may also be treatment targets

NOTE Confidence: 0.28242582

 $00:23:22.288 \rightarrow 00:23:24.400$ specifically for bipolar disorder.

NOTE Confidence: 0.28242582

 $00{:}23{:}24{.}400 \dashrightarrow 00{:}23{:}29{.}687$ And we also collected BOLD fMRI and

NOTE Confidence: 0.28242582

 $00{:}23{:}29{.}687 \dashrightarrow 00{:}23{:}32{.}501$ during an emotional processing task that

NOTE Confidence: 0.28242582

 $00{:}23{:}32{.}501 \dashrightarrow 00{:}23{:}35{.}238$ 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
- $00:23:36.240 \longrightarrow 00:23:40.280$ people are oriented to happy,
- NOTE Confidence: 0.28242582
- $00:23:40.280 \longrightarrow 00:23:42.320$ neutral or fearful faces.
- NOTE Confidence: 0.28242582
- $00:23:42.320 \rightarrow 00:23:45.120$ And our data are currently under review.
- NOTE Confidence: 0.28242582
- $00:23:45.120 \longrightarrow 00:23:47.020$ Biological Psychiatry with Ruth
- NOTE Confidence: 0.28242582
- $00:23:47.020 \longrightarrow 00:23:49.395$ Ash being the lead author.
- NOTE Confidence: 0.28242582
- $00:23:49.400 \rightarrow 00:23:52.433$ And we have people who are controls in black,
- NOTE Confidence: 0.28242582
- $00:23:52.440 \longrightarrow 00:23:54.252$ 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
- $00:23:56.520 \rightarrow 00:23:59.243$ and then people who are who have
- NOTE Confidence: 0.28242582
- $00:23:59.243 \rightarrow 00:24:00.840$ unipolar depression in blue.
- NOTE Confidence: 0.28242582
- $00{:}24{:}00{.}840 \dashrightarrow 00{:}24{:}03{.}283$ And you can see that the response
- NOTE Confidence: 0.28242582
- $00{:}24{:}03{.}283 \dashrightarrow 00{:}24{:}06{.}464$ and the fear task is the same between
- NOTE Confidence: 0.28242582
- $00:24:06.464 \rightarrow 00:24:08.514$ controls and people with MDD.
- NOTE Confidence: 0.28242582
- $00{:}24{:}08{.}520 \dashrightarrow 00{:}24{:}10{.}920$ But people with bipolar disorder
- NOTE Confidence: 0.28242582

 $00:24:10.920 \rightarrow 00:24:13.373$ 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

 $00{:}24{:}16.040 \dashrightarrow 00{:}24{:}18.728$ And when we correlate this response

NOTE Confidence: 0.28242582

 $00:24:18.728 \longrightarrow 00:24:20.072$ with anglify availability,

NOTE Confidence: 0.28242582

 $00:24:20.080 \longrightarrow 00:24:22.300$ we also see significant findings

NOTE Confidence: 0.28242582

 $00:24:22.300 \longrightarrow 00:24:24.520$ in the bipolar group only.

NOTE Confidence: 0.28242582

 $00{:}24{:}24{.}520 \dashrightarrow 00{:}24{:}25{.}756$ 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

 $00{:}24{:}33{.}560 \dashrightarrow 00{:}24{:}37{.}536$ cognitive and bold response measures.

NOTE Confidence: 0.28242582

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

NOTE Confidence: 0.28242582

 $00{:}24{:}38{.}720 \dashrightarrow 00{:}24{:}42{.}360$ I'm evaluating Anglo 5 to see if it

NOTE Confidence: 0.28242582

 $00:24:42.360 \rightarrow 00:24:45.560$ can help us differentiate suicidality

NOTE Confidence: 0.28242582

 $00:24:45.560 \rightarrow 00:24:48.680$ in people with bipolar disorder specifically.

NOTE Confidence: 0.28242582

 $00:24:48.680 \rightarrow 00:24:52.135$ And this RO one started right before COVID.

- NOTE Confidence: 0.28242582
- $00{:}24{:}52{.}135 \dashrightarrow 00{:}24{:}55{.}412$ And so we've not been as successful

 $00:24:55.412 \rightarrow 00:24:56.716$ in these previous studies,

NOTE Confidence: 0.28242582

 $00{:}24{:}56{.}720 \dashrightarrow 00{:}24{:}58{.}440$ but the data collection's ongoing.

NOTE Confidence: 0.28242582

 $00{:}24{:}58{.}440 \dashrightarrow 00{:}25{:}00{.}176$ I'll be happy to present our data

NOTE Confidence: 0.28242582

 $00{:}25{:}00{.}176 \dashrightarrow 00{:}25{:}01{.}479$ in a couple of years,

NOTE Confidence: 0.28242582

 $00{:}25{:}01{.}480 \dashrightarrow 00{:}25{:}04{.}238$ but right now I will switch gears

NOTE Confidence: 0.28242582

 $00:25:04.238 \longrightarrow 00:25:05.920$ and talk about PTSD.

NOTE Confidence: 0.28242582

 $00:25:05.920 \longrightarrow 00:25:07.920$ 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

 $00{:}25{:}15.376 \dashrightarrow 00{:}25{:}17.910$ growing at Yale and in collaboration

NOTE Confidence: 0.28242582

 $00{:}25{:}17{.}910 \dashrightarrow 00{:}25{:}20{.}280$ with the National Center for PTSD.

NOTE Confidence: 0.28242582

 $00{:}25{:}20{.}280 \dashrightarrow 00{:}25{:}23{.}313$ 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

 $00{:}25{:}25{.}635 \dashrightarrow 00{:}25{:}27{.}950$ differentiate people who have PTSD

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

 $00{:}25{:}35{.}174 \dashrightarrow 00{:}25{:}37{.}540$ 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

 $00:25:42.004 \longrightarrow 00:25:43.708$ and it is the only disorder

NOTE Confidence: 0.313723

 $00{:}25{:}43.708 \dashrightarrow 00{:}25{:}45.678$ that we know the etiology for.

NOTE Confidence: 0.313723

 $00{:}25{:}45.680 \dashrightarrow 00{:}25{:}48.320$ There has to have been a traumatic event,

NOTE Confidence: 0.313723

 $00:25:48.320 \longrightarrow 00:25:51.162$ a criterion, a event that has led

NOTE Confidence: 0.313723

 $00:25:51.162 \rightarrow 00:25:54.319$ to this to development of PTSD.

NOTE Confidence: 0.313723

 $00{:}25{:}54{.}320 \dashrightarrow 00{:}25{:}56{.}672$ About 8% of Americans suffer from

NOTE Confidence: 0.313723

 $00{:}25{:}56.672 \dashrightarrow 00{:}25{:}59.386$ PTSD and this number varies between

NOTE Confidence: 0.313723

 $00:25:59.386 \longrightarrow 00:26:01.518$ a few different publications.

NOTE Confidence: 0.313723

 $00:26:01.520 \longrightarrow 00:26:03.236$ It is more prevalent in women,

NOTE Confidence: 0.313723

 $00:26:03.240 \rightarrow 00:26:04.912$ more prevalent in veterans,

 $00:26:04.912 \rightarrow 00:26:08.120$ and it is the only anxiety disorder

NOTE Confidence: 0.313723

 $00{:}26{:}08{.}120 \dashrightarrow 00{:}26{:}10{.}468$ which predicts anxiety related

NOTE Confidence: 0.313723

 $00:26:10.468 \rightarrow 00:26:12.816$ disorder which predicts suicidality

NOTE Confidence: 0.313723

 $00:26:12.816 \rightarrow 00:26:15.519$ independent of other comorbidities.

NOTE Confidence: 0.313723

 $00:26:15.520 \longrightarrow 00:26:18.240$ Unfortunately, there are only two

NOTE Confidence: 0.313723

 $00:26:18.240 \longrightarrow 00:26:20.960$ FDA approved treatments for PTSD.

NOTE Confidence: 0.313723

 $00:26:20.960 \longrightarrow 00:26:24.020$ They're both SSRIs and they're both

NOTE Confidence: 0.313723

 $00:26:24.020 \rightarrow 00:26:27.280$ 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

 $00{:}26{:}29{.}160 \dashrightarrow 00{:}26{:}33{.}157$ about 10% difference as compared to placebo,

NOTE Confidence: 0.313723

 $00{:}26{:}33.160 \dashrightarrow 00{:}26{:}36.260$ smaller effect size than psychotherapy

NOTE Confidence: 0.313723

 $00{:}26{:}36{.}260 \dashrightarrow 00{:}26{:}39{.}360$ and unclear synergy with psychotherapy.

NOTE Confidence: 0.313723

 $00{:}26{:}39{.}360 \dashrightarrow 00{:}26{:}43{.}424$ They are slow to response typical to any

NOTE Confidence: 0.313723

 $00{:}26{:}43.424 \dashrightarrow 00{:}26{:}46.920$ SSRIs of about, you know, two months.

NOTE Confidence: 0.313723

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

- $00:26:47.824 \rightarrow 00:26:49.560$ 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
- $00{:}26{:}50{.}033 \dashrightarrow 00{:}26{:}52{.}398$ If some body has severe symptoms,
- NOTE Confidence: 0.313723
- $00:26:52.400 \rightarrow 00:26:53.273$ they cannot sleep,
- NOTE Confidence: 0.313723
- $00{:}26{:}53{.}273 \dashrightarrow 00{:}26{:}54{.}437$ they cannot work etcetera,
- NOTE Confidence: 0.313723
- 00:26:54.440 --> 00:26:54.745 etcetera.
- NOTE Confidence: 0.313723
- $00:26:54.745 \rightarrow 00:26:57.880$ You want to be able to help them right away.
- NOTE Confidence: 0.313723
- $00{:}26{:}57{.}880 \dashrightarrow 00{:}27{:}00{.}301$ 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
- $00:27:02.566 \longrightarrow 00:27:05.440$ 5 is anxiolytic and could actually
- NOTE Confidence: 0.313723
- $00:27:05.515 \rightarrow 00:27:08.360$ participate in symptomatology of PTSD.
- NOTE Confidence: 0.313723
- $00:27:08.360 \longrightarrow 00:27:10.160$ And all these data come
- NOTE Confidence: 0.313723
- $00:27:10.160 \longrightarrow 00:27:11.240$ from preclinical models.
- NOTE Confidence: 0.313723
- $00:27:11.240 \longrightarrow 00:27:13.886$ There are no data in human before
- NOTE Confidence: 0.313723
- $00:27:13.886 \longrightarrow 00:27:15.440$ we started publishing this.
- NOTE Confidence: 0.313723
- $00:27:15.440 \longrightarrow 00:27:18.104$ So we see that fear conditioning

- NOTE Confidence: 0.313723
- $00{:}27{:}18.104 \dashrightarrow 00{:}27{:}19.880$ is associated with increased

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

NOTE Confidence: 0.313723

 $00{:}27{:}21.560 \dashrightarrow 00{:}27{:}24.362$ Anglo 5 activity leads to enhancement

NOTE Confidence: 0.313723

 $00{:}27{:}24.362 \dashrightarrow 00{:}27{:}26.840$ of contextual fear after stress.

NOTE Confidence: 0.313723

 $00{:}27{:}26.840 \dashrightarrow 00{:}27{:}29.678$ 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

 $00:27:32.240 \rightarrow 00:27:35.240$ post trauma inhibits memory consolidation.

NOTE Confidence: 0.313723

 $00{:}27{:}35{.}240 \dashrightarrow 00{:}27{:}37{.}592$ Our blockaded knock out of Anglo 5

NOTE Confidence: 0.313723

 $00{:}27{:}37{.}592 \dashrightarrow 00{:}27{:}39{.}160$ interferes with fear extinction.

NOTE Confidence: 0.313723

 $00{:}27{:}39{.}160 \dashrightarrow 00{:}27{:}42{.}839$ So these some of these seem against

NOTE Confidence: 0.313723

 $00:27:42.839 \longrightarrow 00:27:44.751$ each other And so we have to be

NOTE Confidence: 0.313723

 $00{:}27{:}44.751 \dashrightarrow 00{:}27{:}46.245$ really careful of when we give

NOTE Confidence: 0.313723

 $00:27:46.245 \rightarrow 00:27:47.760$ Anglo 5 to people with PTSD,

NOTE Confidence: 0.313723

 $00{:}27{:}47.760 \dashrightarrow 00{:}27{:}51.040$ 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

 $00:27:53.810 \rightarrow 00:27:57.360$ 5 or modulate via different pathway.

NOTE Confidence: 0.313723

 $00{:}27{:}57{.}360 \dashrightarrow 00{:}28{:}00{.}600$ And so this is the first study that we did.

NOTE Confidence: 0.313723

 $00{:}28{:}00{.}600 \dashrightarrow 00{:}28{:}04{.}236$ We recruited 16 individuals with PTSD.

NOTE Confidence: 0.313723

 $00:28:04.240 \longrightarrow 00:28:07.000$ They were all unmedicated, 16 age,

NOTE Confidence: 0.313723

 $00{:}28{:}07{.}000 \dashrightarrow 00{:}28{:}10{.}840$ sex and smoking status match controls.

NOTE Confidence: 0.313723

 $00{:}28{:}10.840 \dashrightarrow 00{:}28{:}13.560$ 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

 $00:28:22.375 \rightarrow 00:28:24.800$ to measure and glorify availability.

NOTE Confidence: 0.313723

 $00:28:24.800 \rightarrow 00:28:27.440$ And so our sample was pretty chronic PTSD,

NOTE Confidence: 0.313723

 $00{:}28{:}27{.}440 \dashrightarrow 00{:}28{:}29{.}024$ about 20 years.

NOTE Confidence: 0.313723

 $00:28:29.024 \longrightarrow 00:28:30.080$ On average,

NOTE Confidence: 0.313723

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

NOTE Confidence: 0.313723

 $00:28:32.200 \longrightarrow 00:28:34.825$ which tells you that a lot of

NOTE Confidence: 0.313723

 $00{:}28{:}34{.}825 \dashrightarrow 00{:}28{:}36{.}703$ these individuals were more severe

- NOTE Confidence: 0.313723
- 00:28:36.703 > 00:28:38.573 in their PTSD symptomatology.

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

NOTE Confidence: 0.313723

 $00{:}28{:}42.520 \dashrightarrow 00{:}28{:}44.720$ civilians and some combat veterans.

NOTE Confidence: 0.313723

 $00:28:44.720 \longrightarrow 00:28:47.464$ And then we had six people with

NOTE Confidence: 0.313723

 $00{:}28{:}47{.}464 \dashrightarrow 00{:}28{:}49{.}023$ passive suicidal ideations at

NOTE Confidence: 0.313723

 $00:28:49.023 \rightarrow 00:28:50.598$ the time of pet scanning,

NOTE Confidence: 0.313723

 $00:28:50.600 \longrightarrow 00:28:52.925$ and four reported at least

NOTE Confidence: 0.313723

 $00:28:52.925 \longrightarrow 00:28:54.320$ one suicide attempt.

NOTE Confidence: 0.313723

 $00{:}28{:}54{.}320 \dashrightarrow 00{:}28{:}56{.}156$ And so these are outcome data.

NOTE Confidence: 0.313723

 $00:28:56.160 \longrightarrow 00:28:59.346$ So the top panel is the

NOTE Confidence: 0.313723

 $00:28:59.346 \longrightarrow 00:29:01.676$ PTSD group and the bottom

NOTE Confidence: 0.78575593

 $00{:}29{:}01{.}680 \dashrightarrow 00{:}29{:}03{.}520$ 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

 $00{:}29{:}06{.}800 \dashrightarrow 00{:}29{:}07{.}832$ orange, yellow areas,

NOTE Confidence: 0.78575593

 $00{:}29{:}07{.}832 \dashrightarrow 00{:}29{:}10{.}240$ these are quote UN quote hot areas.

 $00{:}29{:}10{.}240 \dashrightarrow 00{:}29{:}11{.}984$ 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

 $00{:}29{:}15{.}240 \dashrightarrow 00{:}29{:}17{.}184$ And you can visually see higher

NOTE Confidence: 0.78575593

 $00{:}29{:}17.184 \dashrightarrow 00{:}29{:}18.480$ 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

 $00{:}29{:}20{.}280 \dashrightarrow 00{:}29{:}23{.}045$ And that won't lie that we actually

NOTE Confidence: 0.78575593

 $00:29:23.045 \rightarrow 00:29:25.159$ expected low receptor availability

NOTE Confidence: 0.78575593

 $00{:}29{:}25{.}159 \dashrightarrow 00{:}29{:}28{.}323$ given the previous MDD study that NOTE Confidence: 0.78575593

 $00{:}29{:}28{.}323 \dashrightarrow 00{:}29{:}31{.}209$ was published and also thinking in NOTE Confidence: 0.78575593

 $00:29:31.209 \rightarrow 00:29:33.520$ 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

 $00{:}29{:}35{.}934 \dashrightarrow 00{:}29{:}38{.}154$ disorders and so there should be

NOTE Confidence: 0.78575593

 $00:29:38.154 \longrightarrow 00:29:40.318$ less places from Glow 5 to sit.

NOTE Confidence: 0.78575593

 $00{:}29{:}40{.}320 \dashrightarrow 00{:}29{:}42{.}370$ And so it would measure

NOTE Confidence: 0.78575593

 $00:29:42.370 \longrightarrow 00:29:43.600$ low receptor availability,

- NOTE Confidence: 0.78575593
- $00:29:43.600 \rightarrow 00:29:47.156$ but we showed crater across brain regions.

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

NOTE Confidence: 0.78575593

 $00:29:49.424 \rightarrow 00:29:51.622$ regions were our main outcomes,

NOTE Confidence: 0.78575593

 $00:29:51.622 \rightarrow 00:29:55.072$ but we saw this across the whole brain.

NOTE Confidence: 0.78575593

 $00{:}29{:}55{.}072 \dashrightarrow 00{:}29{:}57{.}856$ And Sophie Holmes led the publication of

NOTE Confidence: 0.78575593

 $00{:}29{:}57.856 \dashrightarrow 00{:}30{:}00.880$ this study and when she ran some correlation,

NOTE Confidence: 0.78575593

 $00:30:00.880 \longrightarrow 00:30:03.040$ she saw that high Anglo 5

NOTE Confidence: 0.78575593

 $00:30:03.040 \longrightarrow 00:30:04.480$ availability was associated with

NOTE Confidence: 0.78575593

 $00:30:04.548 \longrightarrow 00:30:06.598$ 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

 $00{:}30{:}09{.}127 \dashrightarrow 00{:}30{:}11.678$ differences in the brains between groups,

NOTE Confidence: 0.78575593

 $00{:}30{:}11{.}680 \dashrightarrow 00{:}30{:}14{.}134$ but it's actually much more interesting

NOTE Confidence: 0.78575593

 $00:30:14.134 \longrightarrow 00:30:17.160$ to see that there's clinical relevance.

NOTE Confidence: 0.78575593

 $00:30:17.160 \longrightarrow 00:30:19.080$ And this finding is really,

NOTE Confidence: 0.78575593

 $00:30:19.080 \rightarrow 00:30:21.592$ really important because avoidance

- $00:30:21.592 \longrightarrow 00:30:23.476$ is something that
- NOTE Confidence: 0.2830151
- $00{:}30{:}26{.}320 \dashrightarrow 00{:}30{:}28{.}100$ prevents people from overcoming
- NOTE Confidence: 0.2830151
- $00:30:28.100 \longrightarrow 00:30:29.435$ 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
- $00:30:31.456 \longrightarrow 00:30:34.032$ etcetera that remind us of the event,
- NOTE Confidence: 0.2830151
- $00:30:34.040 \dashrightarrow 00:30:36.520$ we cannot overcome the PTSD.
- NOTE Confidence: 0.2830151
- $00:30:36.520 \longrightarrow 00:30:38.422$ And maybe on below 5 agents
- NOTE Confidence: 0.2830151
- $00:30:38.422 \rightarrow 00:30:40.320$ could help us with therapy,
- NOTE Confidence: 0.2830151
- $00{:}30{:}40{.}320 \dashrightarrow 00{:}30{:}42{.}119$ may be we can give it prior to
- NOTE Confidence: 0.2830151
- $00:30:42.119 \rightarrow 00:30:43.051$ 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
- $00:30:46.339 \rightarrow 00:30:49.560$ kind of surprised by these findings.
- NOTE Confidence: 0.2830151
- $00:30:49.560 \longrightarrow 00:30:52.598$ And so I had been collaborating with
- NOTE Confidence: 0.2830151
- $00:30:52.598 \rightarrow 00:30:55.376$ the late Ron Duman for some other work.
- NOTE Confidence: 0.2830151
- $00{:}30{:}55{.}376 \dashrightarrow 00{:}30{:}57{.}589$ And I had asked him if he could look
- NOTE Confidence: 0.2830151
- $00:30:57.589 \rightarrow 00:30:59.443$ at the postmortem brain tissue and

 $00:30:59.443 \rightarrow 00:31:01.610$ people with PTSD that he had from

NOTE Confidence: 0.2830151

 $00{:}31{:}01{.}610 \dashrightarrow 00{:}31{:}03{.}841$ 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

 $00:31:05.923 \longrightarrow 00:31:08.156$ or stress related proteins that

NOTE Confidence: 0.2830151

 $00:31:08.156 \dashrightarrow 00:31:10.874$ 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

 $00{:}31{:}13.712 \dashrightarrow 00{:}31{:}15.964$ 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

 $00:31:18.760 \dashrightarrow 00:31:21.056$ people with PTSD in the postmortem NOTE Confidence: 0.2830151

 $00:31:21.056 \rightarrow 00:31:23.396$ 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

 $00{:}31{:}26{.}340 \dashrightarrow 00{:}31{:}27{.}320$ regulating protein.

NOTE Confidence: 0.2830151

 $00:31:27.320 \dashrightarrow 00:31:30.242$ And there's some hypothesis that there's

NOTE Confidence: 0.2830151

 $00{:}31{:}30{.}242 \dashrightarrow 00{:}31{:}32{.}600$ 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

 $00:31:35.664 \rightarrow 00:31:37.917$ 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

 $00{:}31{:}46.040 \dashrightarrow 00{:}31{:}47.240$ And so again,

NOTE Confidence: 0.2830151

 $00{:}31{:}47{.}240 \dashrightarrow 00{:}31{:}49{.}240$ 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

 $00:31:51.503 \longrightarrow 00:31:53.355$ 5 related trafficking protein.

NOTE Confidence: 0.2830151

 $00{:}31{:}53{.}360 \dashrightarrow 00{:}31{:}56{.}356$ And So what we think is happening

NOTE Confidence: 0.2830151

 $00:31:56.360 \longrightarrow 00:31:57.720$ in the healthy brain,

NOTE Confidence: 0.2830151

 $00:31:57.720 \longrightarrow 00:31:59.080$ there's so many receptors,

NOTE Confidence: 0.2830151

 $00:31:59.080 \longrightarrow 00:32:00.840$ some of them are internalized,

NOTE Confidence: 0.2830151

 $00:32:00.840 \dashrightarrow 00:32:03.560$ some of them are in the synaptic space.

NOTE Confidence: 0.2830151

 $00{:}32{:}03{.}560 \dashrightarrow 00{:}32{:}05{.}976$ And so our radioligand as I told you

NOTE Confidence: 0.2830151

 $00{:}32{:}05{.}976 \dashrightarrow 00{:}32{:}08{.}944$ can only bind to the places that to the

NOTE Confidence: 0.2830151

 $00:32:08.944 \rightarrow 00:32:11.280$ receptors that are the synaptic space.

- NOTE Confidence: 0.2830151
- 00:32:11.280 --> 00:32:12.126 In PTSD,
- NOTE Confidence: 0.2830151
- $00:32:12.126 \longrightarrow 00:32:14.241$ we think that they're increased
- NOTE Confidence: 0.2830151
- $00{:}32{:}14.241 \dashrightarrow 00{:}32{:}16.370$ Shank levels which traffic Anglo
- NOTE Confidence: 0.2830151
- $00:32:16.370 \longrightarrow 00:32:18.320$ 5 to the synaptic space.
- NOTE Confidence: 0.2830151
- $00:32:18.320 \dashrightarrow 00:32:20.510$ Now the radioligand has more places
- NOTE Confidence: 0.2830151
- $00{:}32{:}20{.}510 \dashrightarrow 00{:}32{:}22{.}624$ to bind and so we're measuring
- NOTE Confidence: 0.2830151
- $00:32:22.624 \rightarrow 00:32:24.354$ 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
- $00:32:26.680 \rightarrow 00:32:30.474$ but their location changed and this location,
- NOTE Confidence: 0.2830151
- $00:32:30.480 \longrightarrow 00:32:33.186$ this change in location appears to
- NOTE Confidence: 0.2830151
- $00:32:33.186 \longrightarrow 00:32:36.200$ contribute to the avoided symptomatology.
- NOTE Confidence: 0.2830151
- $00{:}32{:}36{.}200 \dashrightarrow 00{:}32{:}36{.}884$ And so,
- NOTE Confidence: 0.2830151
- $00:32:36.884 \rightarrow 00:32:38.594$ given the higher rates of
- NOTE Confidence: 0.2830151
- $00:32:38.594 \dashrightarrow 00:32:40.600$ suicidality in this group as well,
- NOTE Confidence: 0.2830151
- $00:32:40.600 \rightarrow 00:32:42.285$ we proceeded with another study
- NOTE Confidence: 0.2830151

 $00:32:42.285 \rightarrow 00:32:44.690$ that was led by Maggie Davis.

NOTE Confidence: 0.2830151

 $00{:}32{:}44.690 \dashrightarrow 00{:}32{:}47.700$ And we have people with who

NOTE Confidence: 0.2830151

 $00:32:47.700 \longrightarrow 00:32:49.600$ are healthy controls in grey,

NOTE Confidence: 0.2830151

 $00:32:49.600 \dashrightarrow 00:32:51.520$ people with depression and purple.

NOTE Confidence: 0.2830151

 $00{:}32{:}51{.}520 \dashrightarrow 00{:}32{:}53{.}320$ The light purple is people with

NOTE Confidence: 0.2830151

 $00{:}32{:}53{.}320 \dashrightarrow 00{:}32{:}55{.}202$ depression who did not have suicidality

NOTE Confidence: 0.2830151

 $00:32:55.202 \rightarrow 00:32:57.074$ at the time of pet scanning.

NOTE Confidence: 0.2830151

 $00:32:57.080 \rightarrow 00:33:00.032$ And then the darker purple are people who

NOTE Confidence: 0.2830151

 $00{:}33{:}00{.}032 \dashrightarrow 00{:}33{:}02{.}398$ had suicidality at the time of scanning.

NOTE Confidence: 0.2830151

 $00{:}33{:}02{.}400 \dashrightarrow 00{:}33{:}04{.}128$ And then in below are people

NOTE Confidence: 0.2830151

 $00{:}33{:}04{.}128 \dashrightarrow 00{:}33{:}05{.}280$ with PTSD and light.

NOTE Confidence: 0.2830151

 $00{:}33{:}05{.}280 \dashrightarrow 00{:}33{:}07{.}596$ No suicidality time of scanning and

NOTE Confidence: 0.2830151

 $00:33:07.596 \dashrightarrow 00:33:09.959$ 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

 $00{:}33{:}11.269 \dashrightarrow 00{:}33{:}12.520$ show you our pretty images.

NOTE Confidence: 0.2830151

 $00:33:12.520 \rightarrow 00:33:15.348$ So the top panel people with PTSD

 $00:33:15.348 \rightarrow 00:33:18.140$ with suicidality and you can see

NOTE Confidence: 0.2830151

 $00{:}33{:}18{.}140 \dashrightarrow 00{:}33{:}19{.}625$ significantly higher receptor

NOTE Confidence: 0.2830151

00:33:19.625 --> 00:33:21.540 availability in our graph and

NOTE Confidence: 0.2830151

 $00{:}33{:}21{.}540 \dashrightarrow 00{:}33{:}24{.}229$ in this panel as compared to any

NOTE Confidence: 0.2830151

 $00{:}33{:}24{.}229 \dashrightarrow 00{:}33{:}26{.}599$ 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

 $00{:}33{:}29{.}040 \dashrightarrow 00{:}33{:}30{.}992$ is the correlation between

NOTE Confidence: 0.24639197

 $00{:}33{:}34{.}320 \dashrightarrow 00{:}33{:}37{.}572$ and mood symptoms in people with

NOTE Confidence: 0.24639197

 $00:33:37.572 \dashrightarrow 00:33:39.840$ 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

 $00:33:41.760 \rightarrow 00:33:43.196$ with depression were different.

NOTE Confidence: 0.24639197

 $00{:}33{:}43.196 \dashrightarrow 00{:}33{:}45.350$ 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

 $00{:}33{:}47.205 \dashrightarrow 00{:}33{:}49.440$ had greater number of symptoms,

NOTE Confidence: 0.24639197

00:33:49.440 --> 00:33:51.270 but people with depression who

 $00:33:51.270 \rightarrow 00:33:53.233$ had greater receptor availability

NOTE Confidence: 0.24639197

 $00{:}33{:}53{.}233 \dashrightarrow 00{:}33{:}55{.}357$ had actually lower symptoms.

NOTE Confidence: 0.24639197

 $00:33:55.360 \longrightarrow 00:33:56.824$ So here again,

NOTE Confidence: 0.24639197

 $00{:}33{:}56{.}824 \dashrightarrow 00{:}34{:}00{.}300$ 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

 $00{:}34{:}02{.}315 \dashrightarrow 00{:}34{:}04{.}840$ that may overlap in symptomatology

NOTE Confidence: 0.24639197

 $00:34:04.840 \longrightarrow 00:34:07.033$ 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

 $00:34:20.055 \dashrightarrow 00:34:22.365$ predisposition to developing a PTSD?

NOTE Confidence: 0.24639197

 $00{:}34{:}22{.}365 \dashrightarrow 00{:}34{:}25{.}285$ So are people who are born with high

NOTE Confidence: 0.24639197

 $00:34:25.285 \longrightarrow 00:34:27.871$ Anglo 5 levels are more likely to

NOTE Confidence: 0.24639197

 $00{:}34{:}27.871 \dashrightarrow 00{:}34{:}30.600$ develop PTSD upon a traumatic event?

NOTE Confidence: 0.24639197

 $00:34:30.600 \longrightarrow 00:34:33.020$ Or is Anglo 5A regulation

- NOTE Confidence: 0.24639197
- $00:34:33.020 \rightarrow 00:34:34.956$ A consequence of PTSD?

 $00{:}34{:}34{.}960 \dashrightarrow 00{:}34{:}37{.}534$ Because a lot of people have

NOTE Confidence: 0.24639197

 $00:34:37.534 \rightarrow 00:34:39.720$ significant trauma in their life,

NOTE Confidence: 0.24639197

 $00:34:39.720 \longrightarrow 00:34:42.720$ but not all of them or most of

NOTE Confidence: 0.24639197

 $00:34:42.720 \rightarrow 00:34:45.640$ them will develop PTSD symptoms.

NOTE Confidence: 0.24639197

 $00{:}34{:}45{.}640 \dashrightarrow 00{:}34{:}48{.}382$ 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

 $00{:}34{:}51{.}529 \dashrightarrow 00{:}34{:}54{.}104$ Molecular Psychiatry and Ruth Ashe

NOTE Confidence: 0.24639197

 $00{:}34{:}54{.}104 \dashrightarrow 00{:}34{:}56{.}792$ led the studies in animal models.

NOTE Confidence: 0.24639197

 $00:34:56.800 \rightarrow 00:34:58.116$ They tried to do this in human,

NOTE Confidence: 0.24639197

 $00{:}34{:}58{.}120 \dashrightarrow 00{:}35{:}00{.}028$ but it provided impossible to identify

NOTE Confidence: 0.24639197

 $00:35:00.028 \dashrightarrow 00:35:02.148$ an emergency room people who had a NOTE Confidence: 0.24639197

 $00{:}35{:}02.148 \dashrightarrow 00{:}35{:}03.463$ traumatic event and then followed

NOTE Confidence: 0.24639197

 $00:35:03.463 \dashrightarrow 00:35:05.528$ them for months to see if they would NOTE Confidence: 0.24639197

 $00:35:05.528 \rightarrow 00:35:06.976$ develop PTSD and scan everybody.

 $00:35:06.976 \dashrightarrow 00:35:10.624$ And so Ruth took on the study in

NOTE Confidence: 0.24639197

 $00{:}35{:}10.624 \dashrightarrow 00{:}35{:}13.320$ rats and we administered stress

NOTE Confidence: 0.24639197

 $00:35:13.320 \rightarrow 00:35:15.560$ enhanced fear learning paradigm.

NOTE Confidence: 0.24639197

 $00{:}35{:}15{.}560 \dashrightarrow 00{:}35{:}17{.}558$ And so after the animal survived,

NOTE Confidence: 0.24639197

 $00{:}35{:}17.560 \dashrightarrow 00{:}35{:}19.640$ they acclimated for a bit.

NOTE Confidence: 0.24639197

 $00:35:19.640 \rightarrow 00:35:22.520$ Then they participate in pet scanning,

NOTE Confidence: 0.24639197

 $00:35:22.520 \longrightarrow 00:35:25.880$ daily handling and then Ruth

NOTE Confidence: 0.24639197

 $00:35:25.880 \dashrightarrow 00:35:29.240$ did behavioral testing and then

NOTE Confidence: 0.24639197

 $00{:}35{:}29{.}352 \dashrightarrow 00{:}35{:}30{.}546$ 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

 $00{:}35{:}32{.}784 \dashrightarrow 00{:}35{:}34{.}520$ the animals were shocked

NOTE Confidence: 0.59004176

 $00{:}35{:}36{.}560 \dashrightarrow 00{:}35{:}38{.}765$ and then the next day there was no shock

NOTE Confidence: 0.59004176

 $00{:}35{:}38{.}765 \dashrightarrow 00{:}35{:}40{.}862$ in animals and they were shocked again

NOTE Confidence: 0.59004176

 $00{:}35{:}40.862 \dashrightarrow 00{:}35{:}43.398$ the 3rd day and no shock on the 4th day.

NOTE Confidence: 0.59004176

 $00:35:43.400 \rightarrow 00:35:46.066$ And so this is encephal paradigm

NOTE Confidence: 0.59004176

 $00:35:46.066 \rightarrow 00:35:49.196$ where the shock is not,

- NOTE Confidence: 0.59004176
- $00{:}35{:}49{.}200 \dashrightarrow 00{:}35{:}50{.}838$ the number of shocks is not to

 $00{:}35{:}50{.}838 \dashrightarrow 00{:}35{:}52{.}465$ the extent that all animals are

NOTE Confidence: 0.59004176

 $00:35:52.465 \rightarrow 00:35:54.199$ going to develop PTC type symptoms,

NOTE Confidence: 0.59004176

 $00:35:54.200 \rightarrow 00:35:55.544$ there's going to be a spread

NOTE Confidence: 0.59004176

 $00:35:55.544 \rightarrow 00:35:56.840$ like just like in humans.

NOTE Confidence: 0.59004176

 $00{:}35{:}56{.}840 \dashrightarrow 00{:}35{:}59{.}552$ So some animals are going to be resilient

NOTE Confidence: 0.59004176

 $00:35:59.552 \rightarrow 00:36:02.679$ and some animals are going to be vulnerable.

NOTE Confidence: 0.59004176

 $00:36:02.680 \longrightarrow 00:36:06.075$ And we started seeing sex differences between

NOTE Confidence: 0.59004176

 $00{:}36{:}06.075 \dashrightarrow 00{:}36{:}08.838$ behaviours in animals who were shocked.

NOTE Confidence: 0.54787356

 $00{:}36{:}11{.}360 \dashrightarrow 00{:}36{:}14{.}174$ And then Ruth also divided the animals

NOTE Confidence: 0.54787356

 $00{:}36{:}14.174 \dashrightarrow 00{:}36{:}17.160$ 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

 $00:36:20.562 \dashrightarrow 00:36:23.534$ their shock in the in their freezing.

NOTE Confidence: 0.54787356

 $00{:}36{:}23{.}534 \dashrightarrow 00{:}36{:}25{.}824$ And she saw sex differences

NOTE Confidence: 0.54787356

 $00:36:25.824 \rightarrow 00:36:28.080$ in those groups as well.

00:36:28.080 --> 00:36:29.600 And then in PET scanning,

NOTE Confidence: 0.54787356

 $00:36:29.600 \longrightarrow 00:36:32.360$ we saw that actually receptor

NOTE Confidence: 0.54787356

 $00:36:32.360 \longrightarrow 00:36:34.568$ availability was not different

NOTE Confidence: 0.54787356

 $00:36:34.568 \rightarrow 00:36:37.124$ between control groups and groups

NOTE Confidence: 0.54787356

 $00{:}36{:}37{.}124 \dashrightarrow 00{:}36{:}39{.}519$ 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

 $00:36:46.520 \longrightarrow 00:36:48.080$ at least in this work,

NOTE Confidence: 0.54787356

 $00{:}36{:}48.080 \dashrightarrow 00{:}36{:}50.520$ but did increase in animals

NOTE Confidence: 0.54787356

 $00{:}36{:}50{.}520 \dashrightarrow 00{:}36{:}52{.}472$ as a consequence of

NOTE Confidence: 0.4481057

 $00{:}36{:}54{.}640 \dashrightarrow 00{:}36{:}57{.}400$ of foot shock of stress.

NOTE Confidence: 0.4481057

 $00{:}36{:}57{.}400 \dashrightarrow 00{:}37{:}00{.}410$ And again we saw some stress sex

NOTE Confidence: 0.4481057

 $00{:}37{:}00{.}410 \dashrightarrow 00{:}37{:}02{.}185$ differences And the freezing on day

NOTE Confidence: 0.4481057

 $00:37:02.185 \longrightarrow 00:37:04.720$ 2 on the day that animals were not

NOTE Confidence: 0.4481057

 $00:37:04.720 \dashrightarrow 00:37:06.952$ shocked is related to fear memory.

 $00:37:06.960 \longrightarrow 00:37:09.865$ So it's after the traumatic event when

NOTE Confidence: 0.4481057

 $00{:}37{:}09{.}865 \dashrightarrow 00{:}37{:}11{.}985$ the animals are being put back in the

NOTE Confidence: 0.4481057

 $00:37:11.985 \dashrightarrow 00:37:13.895$ 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

 $00{:}37{:}16.098 \dashrightarrow 00{:}37{:}17.684$ freezing are they participating in.

NOTE Confidence: 0.4481057

 $00:37:17.684 \dashrightarrow 00:37:20.358$ And so the greater the freezing behavior,

NOTE Confidence: 0.4481057

 $00{:}37{:}20{.}360 \dashrightarrow 00{:}37{:}23{.}000$ the greater receptor availability and

NOTE Confidence: 0.4481057

 $00:37:23.000 \rightarrow 00:37:26.120$ again some sex differences in that.

NOTE Confidence: 0.4481057

 $00{:}37{:}26.120 \dashrightarrow 00{:}37{:}30.720$ And so looking at some more recent literature

NOTE Confidence: 0.4481057

 $00:37:30.720 \longrightarrow 00:37:32.556$ and back at some other literature,

NOTE Confidence: 0.4481057

 $00{:}37{:}32{.}560 \dashrightarrow 00{:}37{:}35{.}712$ there is some evidence to support Anglo 5

NOTE Confidence: 0.4481057

 $00{:}37{:}35{.}712 \dashrightarrow 00{:}37{:}38{.}425$ of regulation in response to PTSD events.

NOTE Confidence: 0.4481057

 $00{:}37{:}38{.}425 \dashrightarrow 00{:}37{:}40{.}910$ And so this work was done right

NOTE Confidence: 0.4481057

 $00{:}37{:}40{.}992 \dashrightarrow 00{:}37{:}43{.}260$ around the time that we published

NOTE Confidence: 0.4481057

 $00:37:43.260 \longrightarrow 00:37:45.760$ our work only in male models,

- $00:37:45.760 \longrightarrow 00:37:48.935$ 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
- $00:37:52.370 \longrightarrow 00:37:54.920$ who develop PTSD type symptoms.
- NOTE Confidence: 0.4481057
- $00{:}37{:}54{.}920 \dashrightarrow 00{:}37{:}57{.}594$ 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
- $00{:}37{:}58{.}360 \dashrightarrow 00{:}38{:}00{.}220$ blocked this response,
- NOTE Confidence: 0.4481057
- $00:38:00.220 \longrightarrow 00:38:02.080$ this freezing response.
- NOTE Confidence: 0.4481057
- $00:38:02.080 \rightarrow 00:38:05.536$ 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
- $00:38:08.834 \dashrightarrow 00:38:12.313$ had greater Mglu 5 availability upon retest.
- NOTE Confidence: 0.4481057
- $00{:}38{:}12{.}320 \dashrightarrow 00{:}38{:}14{.}876$ But MPEP had blocked this effect.
- NOTE Confidence: 0.4481057
- $00:38:14.880 \longrightarrow 00:38:16.372$ So the study actually,
- NOTE Confidence: 0.4481057
- 00:38:16.372 --> 00:38:17.118 you know,
- NOTE Confidence: 0.4481057
- $00:38:17.120 \longrightarrow 00:38:19.620$ did some treatment and showed
- NOTE Confidence: 0.4481057
- $00{:}38{:}19.620 \dashrightarrow 00{:}38{:}22.560$ that treatment with Mglu 5 NAMM
- NOTE Confidence: 0.4481057
- $00:38:22.560 \rightarrow 00:38:24.512$ could actually be beneficial.

- NOTE Confidence: 0.4481057
- $00:38:24.520 \longrightarrow 00:38:27.976$ And so we also did our own work

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

 $00:38:36.280 \longrightarrow 00:38:38.345$ And we did this a while ago

NOTE Confidence: 0.59582347

 $00{:}38{:}38{.}345 \dashrightarrow 00{:}38{:}40{.}878$ 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

 $00:38:44.860 \dashrightarrow 00:38:48.136$ wanted to modulate Mglo 5 not directly,

NOTE Confidence: 0.59582347

 $00:38:48.136 \dashrightarrow 00:38:50.876$ but via modulation of glutamate.

NOTE Confidence: 0.59582347

 $00{:}38{:}50{.}880 \dashrightarrow 00{:}38{:}53{.}553$ And I think all of you know at this

NOTE Confidence: 0.59582347

 $00{:}38{:}53{.}553 \dashrightarrow 00{:}38{:}55{.}978$ point that 7 acetic doses of ketamine

NOTE Confidence: 0.59582347

 $00:38:55.978 \longrightarrow 00:38:58.799$ 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 an
aesthetic doses do not

NOTE Confidence: 0.59582347

 $00:39:02.440 \longrightarrow 00:39:04.560$ lead to a surge in glutamate.

NOTE Confidence: 0.59582347

 $00{:}39{:}04{.}560 \dashrightarrow 00{:}39{:}08{.}200$ And there were studies done with Mrs.

 $00:39:08.200 \rightarrow 00:39:10.200$ showing this is proton, Mrs.

NOTE Confidence: 0.59582347

 $00:39:10.200 \rightarrow 00:39:12.080$ showing that administration of ketamine

NOTE Confidence: 0.59582347

 $00{:}39{:}12.080 \dashrightarrow 00{:}39{:}14.852$ 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

 $00:39:17.528 \dashrightarrow 00:39:21.264$ group did a study with carbon 13 Mrs.

NOTE Confidence: 0.59582347

 $00{:}39{:}21{.}264 \dashrightarrow 00{:}39{:}23{.}408$ showing increases in glutamate

NOTE Confidence: 0.59582347

 $00{:}39{:}23{.}408 \dashrightarrow 00{:}39{:}25{.}656$ levels after an esthetic doses

NOTE Confidence: 0.59582347

 $00:39:25.656 \longrightarrow 00:39:28.596$ of ketamine in animal models.

NOTE Confidence: 0.59582347

 $00{:}39{:}28.600 \dashrightarrow 00{:}39{:}31.274$ And so this was our study day,

NOTE Confidence: 0.59582347

 $00:39:31.280 \longrightarrow 00:39:32.588$ our study design, sorry.

NOTE Confidence: 0.59582347

 $00:39:32.588 \rightarrow 00:39:34.550$ 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

 $00:39:36.396 \longrightarrow 00:39:38.048$ then we do a baseline scan and

NOTE Confidence: 0.59582347

 $00:39:38.048 \longrightarrow 00:39:39.519$ a ketamine scan the same day.

NOTE Confidence: 0.59582347

 $00:39:39.520 \longrightarrow 00:39:41.956$ And then we invited people 24 hours

NOTE Confidence: 0.59582347

00:39:41.956 - 00:39:43.689 later to participate in another

 $00:39:43.689 \rightarrow 00:39:45.920$ 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

 $00:39:48.332 \rightarrow 00:39:50.030$ greatest antidepressant response

NOTE Confidence: 0.59582347

 $00:39:50.030 \dashrightarrow 00:39:51.560$ of ketamine administration.

NOTE Confidence: 0.59582347

 $00{:}39{:}51{.}560 \dashrightarrow 00{:}39{:}54{.}386$ And so we thought that administration

NOTE Confidence: 0.59582347

 $00{:}39{:}54{.}386 \dashrightarrow 00{:}39{:}56{.}942$ of ketamine would lead to a

NOTE Confidence: 0.59582347

 $00:39:56.942 \dashrightarrow 00:39:59.137$ glutamate surge which would down

NOTE Confidence: 0.59582347

 $00:39:59.137 \rightarrow 00:40:01.040$ regulate and Glu fives immediately.

NOTE Confidence: 0.59582347

 $00{:}40{:}01{.}040 \dashrightarrow 00{:}40{:}03{.}691$ But that would lead to an up

NOTE Confidence: 0.59582347

 $00:40:03.691 \longrightarrow 00:40:05.825$ regulation of Glu 524 hours later

NOTE Confidence: 0.59582347

 $00{:}40{:}05.825 \dashrightarrow 00{:}40{:}07.955$ 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

 $00{:}40{:}13.920 \dashrightarrow 00{:}40{:}15.720$ More places for Anglo 5 to sit on

NOTE Confidence: 0.59582347

 $00{:}40{:}15.720 \dashrightarrow 00{:}40{:}18.055$ and so there will be greater angle 5

 $00:40:18.055 \rightarrow 00:40:20.141$ availability and it will be related

NOTE Confidence: 0.59582347

 $00:40:20.141 \rightarrow 00:40:22.482$ to instepressing response and so on.

NOTE Confidence: 0.59582347

 $00:40:22.482 \longrightarrow 00:40:23.978$ The ketamine day subjects

NOTE Confidence: 0.59582347

 $00{:}40{:}23.978 \dashrightarrow 00{:}40{:}25.560$ participating to PET scans.

NOTE Confidence: 0.59582347

 $00{:}40{:}25{.}560 \dashrightarrow 00{:}40{:}26{.}880$ That radio tracer was

NOTE Confidence: 0.59582347

 $00:40:26.880 \longrightarrow 00:40:28.200$ administered as a bolus,

NOTE Confidence: 0.59582347

 $00{:}40{:}28.200 \dashrightarrow 00{:}40{:}30.756$ People are scanned for 90 minutes,

NOTE Confidence: 0.59582347

 $00{:}40{:}30.760 \dashrightarrow 00{:}40{:}33.256$ they had a break and then we administered

NOTE Confidence: 0.59582347

 $00{:}40{:}33.256 \dashrightarrow 00{:}40{:}35.691$ the radio tracer followed by ketamine

NOTE Confidence: 0.59582347

 $00{:}40{:}35.691 \dashrightarrow 00{:}40{:}37.435$ bolus plus infusion paradigm.

NOTE Confidence: 0.59582347

 $00{:}40{:}37{.}440 \dashrightarrow 00{:}40{:}39{.}500$ So this administration gives a

NOTE Confidence: 0.59582347

 $00{:}40{:}39{.}500 \dashrightarrow 00{:}40{:}42{.}666$ bit more ketamine than the quote

NOTE Confidence: 0.59582347

 $00:40:42.666 \rightarrow 00:40:45.952$ typical antidepressant 40 minute

NOTE Confidence: 0.59582347

 $00:40:45.952 \longrightarrow 00:40:47.560$ just infusion administration.

NOTE Confidence: 0.59582347

 $00{:}40{:}47{.}560 \dashrightarrow 00{:}40{:}51{.}093$ But we really given the expense of pet,

NOTE Confidence: 0.59582347

 $00:40:51.093 \rightarrow 00:40:52.758$ the need for a line,

- NOTE Confidence: 0.59582347
- $00:40:52.760 \rightarrow 00:40:55.063$ the radiation we give the subjects the

 $00{:}40{:}55{.}063 \dashrightarrow 00{:}40{:}57{.}639$ time the subjects contribute to our studies.

NOTE Confidence: 0.59582347

 $00:40:57.640 \longrightarrow 00:40:59.992$ We really wanted to make sure that

NOTE Confidence: 0.59582347

 $00:40:59.992 \rightarrow 00:41:02.185$ we're going to see significant findings

NOTE Confidence: 0.59582347

 $00:41:02.185 \rightarrow 00:41:04.160$ if there were significant findings.

NOTE Confidence: 0.59582347

 $00:41:04.160 \longrightarrow 00:41:06.437$ So we gave a bit of a higher dose.

NOTE Confidence: 0.59582347

 $00:41:06.440 \longrightarrow 00:41:09.500$ So we had 13 people with

NOTE Confidence: 0.59582347

 $00:41:09.500 \longrightarrow 00:41:10.520$ depression participate.

NOTE Confidence: 0.59582347

 $00:41:10.520 \longrightarrow 00:41:13.238$ They you can see that they're

NOTE Confidence: 0.59582347

 $00{:}41{:}13{.}240 \dashrightarrow 00{:}41{:}15{.}034$ 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

 $00{:}41{:}16.512 \dashrightarrow 00{:}41{:}18.272$ that we recruit but we were excluding

NOTE Confidence: 0.59582347

 $00:41:18.272 \longrightarrow 00:41:19.840$ people with any suicidality.

NOTE Confidence: 0.59582347

 $00{:}41{:}19{.}840 \dashrightarrow 00{:}41{:}21{.}360$ We were really, really,

NOTE Confidence: 0.59582347

 $00{:}41{:}21{.}360 \dashrightarrow 00{:}41{:}23{.}074$ really careful about making sure

 $00:41:23.074 \rightarrow 00:41:24.664$ that people who are participating

NOTE Confidence: 0.59582347

 $00:41:24.664 \longrightarrow 00:41:26.781$ 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

 $00{:}41{:}28.811 \dashrightarrow 00{:}41{:}30.932$ 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

 $00{:}41{:}35{.}664 \dashrightarrow 00{:}41{:}38{.}548$ We really wanted to make sure that

NOTE Confidence: 0.59582347

 $00:41:38.548 \longrightarrow 00:41:40.800$ these were subjects who could be

NOTE Confidence: 0.59582347

 $00{:}41{:}40.800 \dashrightarrow 00{:}41{:}43.003$ able to complete the study without

NOTE Confidence: 0.59582347

 $00{:}41{:}43.003 \dashrightarrow 00{:}41{:}45.421$ 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

 $00:41:50.560 \longrightarrow 00:41:51.658$ our first study.

NOTE Confidence: 0.59582347

 $00{:}41{:}51{.}658 \dashrightarrow 00{:}41{:}54{.}220$ 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

 $00:41:57.160 \longrightarrow 00:42:00.240$ And so the top panel is MRI scans,

- NOTE Confidence: 0.7197303
- $00:42:00.240 \longrightarrow 00:42:02.968$ the middle panel is our baseline PET and

 $00:42:02.968 \rightarrow 00:42:05.599$ 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

 $00:42:07.475 \longrightarrow 00:42:08.975$ decrease in receptor availability

NOTE Confidence: 0.7197303

 $00{:}42{:}08{.}975 \dashrightarrow 00{:}42{:}10{.}920$ after administration of ketamine.

NOTE Confidence: 0.7197303

 $00{:}42{:}10{.}920 \dashrightarrow 00{:}42{:}13{.}472$ And if you think back to slide may be

NOTE Confidence: 0.7197303

 $00{:}42{:}13.472 \dashrightarrow 00{:}42{:}17.056$ 8 or 9 where I showed you there are no

NOTE Confidence: 0.7197303

 $00{:}42{:}17.056 \dashrightarrow 00{:}42{:}19.824$ variation of Unglu 5 and that in the

NOTE Confidence: 0.7197303

 $00{:}42{:}19{.}824 \dashrightarrow 00{:}42{:}22{.}680$ afternoon Unglu 5 levels are lower as it is.

NOTE Confidence: 0.7197303

 $00:42:22.680 \longrightarrow 00:42:23.700$ Given that we were measuring

NOTE Confidence: 0.7197303

 $00:42:23.700 \longrightarrow 00:42:24.516$ this in the afternoon,

NOTE Confidence: 0.7197303

 $00:42:24.520 \rightarrow 00:42:30.408$ we're likely sub estimating how much display,

NOTE Confidence: 0.7197303

 $00:42:30.408 \longrightarrow 00:42:32.616$ 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

 $00:42:33.720 \rightarrow 00:42:36.760$ So this 20 to 40% change the way measured,

 $00:42:36.760 \longrightarrow 00:42:38.440$ it's probably even greater.

NOTE Confidence: 0.7197303

 $00{:}42{:}38{.}440 \dashrightarrow 00{:}42{:}41{.}107$ And this was across all brain regions

NOTE Confidence: 0.7197303

 $00{:}42{:}41.107 \dashrightarrow 00{:}42{:}42.662$ including the cerebellum where

NOTE Confidence: 0.7197303

 $00:42:42.662 \rightarrow 00:42:44.720$ people use as a reference tissue,

NOTE Confidence: 0.7197303

 $00{:}42{:}44.720 \dashrightarrow 00{:}42{:}47.125$ 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

 $00:42:50.231 \rightarrow 00:42:52.719$ for measuring anglify availability.

NOTE Confidence: 0.7197303

 $00:42:52.720 \rightarrow 00:42:57.640$ And contrary to our initial hypothesis,

NOTE Confidence: 0.7197303

 $00{:}42{:}57{.}640 \dashrightarrow 00{:}43{:}00{.}440$ 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

 $00{:}43{:}03.870 \dashrightarrow 00{:}43{:}06.830$ availability and people with who are

NOTE Confidence: 0.7197303

 $00{:}43{:}06{.}830 \dashrightarrow 00{:}43{:}10{.}439$ controls and and people who are depressed.

NOTE Confidence: 0.7197303

 $00{:}43{:}10{.}440 \dashrightarrow 00{:}43{:}14{.}222$ And so again we were surprised and

NOTE Confidence: 0.7197303

 $00:43:14.222 \rightarrow 00:43:16.732$ given that we expected increases

NOTE Confidence: 0.7197303

 $00:43:16.732 \longrightarrow 00:43:18.793$ in Anglophile availability and

NOTE Confidence: 0.7197303

 $00:43:18.793 \rightarrow 00:43:21.558$ all of the initial studies,
- NOTE Confidence: 0.7197303
- $00:43:21.560 \rightarrow 00:43:23.996$ the mechanistic studies that I showed you

NOTE Confidence: 0.7197303

 $00{:}43{:}24.000 \dashrightarrow 00{:}43{:}26.758$ helped us understand what is going on.

NOTE Confidence: 0.7197303

 $00:43:26.760 \rightarrow 00:43:29.955$ And so on the left we have a typical

NOTE Confidence: 0.7197303

 $00:43:29.955 \rightarrow 00:43:32.640$ situation where person has had no drug.

NOTE Confidence: 0.7197303

 $00:43:32.640 \longrightarrow 00:43:34.365$ 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

 $00{:}43{:}38{.}403 \dashrightarrow 00{:}43{:}41{.}437$ 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

 $00{:}43{:}43{.}360 \dashrightarrow 00{:}43{:}45{.}466$ we think there's greater glutamate release

NOTE Confidence: 0.7197303

 $00{:}43{:}45{.}466 \dashrightarrow 00{:}43{:}48{.}517$ which is going to down regulate on Glu fives.

NOTE Confidence: 0.7197303

 $00{:}43{:}48{.}520 \dashrightarrow 00{:}43{:}50{.}207$ So now more on Glu fives are

NOTE Confidence: 0.7197303

 $00{:}43{:}50{.}207 \dashrightarrow 00{:}43{:}52{.}080$ going to be an internal space.

NOTE Confidence: 0.7197303

 $00{:}43{:}52.080 \dashrightarrow 00{:}43{:}54.342$ Given that the radio ligand cannot

NOTE Confidence: 0.7197303

 $00{:}43{:}54{.}342 \dashrightarrow 00{:}43{:}55{.}473$ measure internalized receptors,

NOTE Confidence: 0.7197303

 $00:43:55.480 \rightarrow 00:43:58.120$ we're measuring low receptor availability.

NOTE Confidence: 0.7197303

 $00:43:58.120 \longrightarrow 00:44:00.838$ So we're thinking that this low

NOTE Confidence: 0.7197303

 $00:44:00.838 \longrightarrow 00:44:02.650$ receptor availability is indeed

NOTE Confidence: 0.7197303

 $00:44:02.722 \longrightarrow 00:44:05.208$ receptor trafficking to the

NOTE Confidence: 0.7197303

 $00:44:05.208 \longrightarrow 00:44:07.828$ internalized space and potentially is

NOTE Confidence: 0.7197303

 $00:44:07.828 \rightarrow 00:44:10.560$ associated with changes in hematology.

NOTE Confidence: 0.7197303

 $00:44:10.560 \longrightarrow 00:44:13.115$ And so of course they told you

NOTE Confidence: 0.7197303

 $00{:}44{:}13.115 \dashrightarrow 00{:}44{:}13.719$ to me it's really,

NOTE Confidence: 0.7197303

 $00:44:13.720 \rightarrow 00:44:15.845$ really important to understand the

NOTE Confidence: 0.7197303

 $00:44:15.845 \rightarrow 00:44:17.970$ link between what we're seeing

NOTE Confidence: 0.7197303

 $00:44:18.043 \longrightarrow 00:44:19.678$ in the brain to symptoms.

NOTE Confidence: 0.7197303

 $00{:}44{:}19.680 \dashrightarrow 00{:}44{:}22.554$ And we saw a significant association

NOTE Confidence: 0.7197303

 $00:44:22.554 \rightarrow 00:44:25.599$ between decreased and Angle 5 availability

NOTE Confidence: 0.7197303

 $00{:}44{:}25.600 \dashrightarrow 00{:}44{:}27.835$ and decrease in symptomatology in

NOTE Confidence: 0.7197303

 $00:44:27.835 \rightarrow 00:44:30.760$ 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

 $00:44:34.964 \longrightarrow 00:44:37.974$ 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

 $00:44:41.320 \longrightarrow 00:44:45.340$ And so between the PTSD study

NOTE Confidence: 0.7197303

 $00:44:45.340 \longrightarrow 00:44:48.056$ and this ketamine study,

NOTE Confidence: 0.7197303

 $00:44:48.056 \rightarrow 00:44:51.420$ we are seeing the Anglo 5 May

NOTE Confidence: 0.7197303

 $00:44:51.420 \longrightarrow 00:44:53.045$ not only help us differentiate

NOTE Confidence: 0.7197303

00:44:53.045 --> 00:44:54.639 between different disorders,

NOTE Confidence: 0.7197303

 $00{:}44{:}54{.}640 \dashrightarrow 00{:}44{:}57{.}237$ but potentially has a role in suicidality.

NOTE Confidence: 0.7197303

 $00{:}44{:}57{.}240 \dashrightarrow 00{:}44{:}59{.}214$ And I'm also seeing some of this

NOTE Confidence: 0.7197303

 $00:44:59.214 \rightarrow 00:45:01.322$ in my bipolar work that I'm not

NOTE Confidence: 0.7197303

 $00{:}45{:}01{.}322 \dashrightarrow 00{:}45{:}02{.}518$ ready to present yet.

NOTE Confidence: 0.7197303

 $00{:}45{:}02.520 \dashrightarrow 00{:}45{:}05.040$ But going back to the literature,

NOTE Confidence: 0.7197303

 $00{:}45{:}05{.}040 \dashrightarrow 00{:}45{:}05{.}880$ there's some

NOTE Confidence: 0.44133765

 $00:45:08.200 \rightarrow 00:45:10.916$ support for alterations in Homer which is

NOTE Confidence: 0.44133765

 $00{:}45{:}10.916 \dashrightarrow 00{:}45{:}12.759$ another trafficking protein for Anglo 5

NOTE Confidence: 0.44133765

 $00:45:12.760 \longrightarrow 00:45:15.478$ 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

 $00{:}45{:}22.800 \dashrightarrow 00{:}45{:}25.792$ in people with who died by suicide.

NOTE Confidence: 0.44133765

 $00{:}45{:}25.792 \dashrightarrow 00{:}45{:}27.732$ Both ketamine and lithium exert

NOTE Confidence: 0.44133765

 $00{:}45{:}27.732 \dashrightarrow 00{:}45{:}30.414$ into suicidal actions via influences

NOTE Confidence: 0.44133765

 $00:45:30.414 \longrightarrow 00:45:32.079$ and glutamatergic system.

NOTE Confidence: 0.44133765

 $00{:}45{:}32.080 \dashrightarrow 00{:}45{:}34.376$ And now we're having evidence from our NOTE Confidence: 0.44133765

 $00{:}45{:}34{.}376 \dashrightarrow 00{:}45{:}36{.}863$ group showing that greater extent of

NOTE Confidence: 0.44133765

 $00:45:36.863 \dashrightarrow 00:45:39.869$ Glu 5 down regulation is supporting NOTE Confidence: 0.44133765

 $00{:}45{:}39{.}869 \dashrightarrow 00{:}45{:}42{.}919$ greater relief from suicidal thinking. NOTE Confidence: 0.44133765

1011 Connuclice. 0.44155105

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

 $00{:}45{:}51.782 \dashrightarrow 00{:}45{:}54.206$ in various populations and there

- NOTE Confidence: 0.44133765
- $00:45:54.206 \rightarrow 00:45:56.290$ could be differentially expressed

NOTE Confidence: 0.44133765

 $00:45:56.290 \rightarrow 00:45:59.030$ and differentially important across

NOTE Confidence: 0.44133765

 $00:45:59.030 \longrightarrow 00:46:00.400$ different populations.

NOTE Confidence: 0.44133765

 $00{:}46{:}00{.}400 \dashrightarrow 00{:}46{:}02{.}720$ 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

 $00:46:08.280 \rightarrow 00:46:11.800$ just a couple more slides that have been,

NOTE Confidence: 0.44133765

 $00:46:11.800 \longrightarrow 00:46:14.170$ 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

 $00:46:16.691 \rightarrow 00:46:18.435$ for some collaborators especially

NOTE Confidence: 0.44133765

 $00{:}46{:}18.435 \dashrightarrow 00{:}46{:}20.600$ in the studies of pain.

NOTE Confidence: 0.44133765

 $00:46:20.600 \longrightarrow 00:46:23.678$ So a lot of, you know,

NOTE Confidence: 0.44133765

 $00:46:23.680 \longrightarrow 00:46:24.568$ you know,

NOTE Confidence: 0.44133765

 $00{:}46{:}24.568 \dashrightarrow 00{:}46{:}26.788$ there's interplay between pain and

NOTE Confidence: 0.44133765

 $00:46:26.788 \rightarrow 00:46:27.676 \mod$ symptoms,

NOTE Confidence: 0.44133765

 $00:46:27.680 \rightarrow 00:46:30.398$ but also between pain and suicidality.

NOTE Confidence: 0.44133765

 $00{:}46{:}30{.}400 \dashrightarrow 00{:}46{:}32{.}927$ And what we're seeing with our Angular

NOTE Confidence: 0.44133765

 $00:46:32.927 \longrightarrow 00:46:36.283$ 5 work in people is higher receptor

NOTE Confidence: 0.44133765

 $00:46:36.283 \rightarrow 00:46:37.930$ availability across diagnostic

NOTE Confidence: 0.44133765

 $00{:}46{:}37{.}930 \dashrightarrow 00{:}46{:}40{.}874$ groups in people who reported chronic

NOTE Confidence: 0.44133765

 $00:46:40.874 \rightarrow 00:46:43.716$ pain at the time of PET scanning.

NOTE Confidence: 0.44133765

 $00:46:43.720 \longrightarrow 00:46:45.477$ So they're in the top panel as

NOTE Confidence: 0.44133765

 $00:46:45.477 \rightarrow 00:46:47.039$ compared to healthy control groups.

NOTE Confidence: 0.44133765

 $00{:}46{:}47.040 \dashrightarrow 00{:}46{:}49.630$ And I just showed you that suicidality

NOTE Confidence: 0.44133765

 $00{:}46{:}49{.}630 \dashrightarrow 00{:}46{:}51{.}632$ is associated with higher angular

NOTE Confidence: 0.44133765

 $00:46:51.632 \longrightarrow 00:46:53.276$ 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

 $00:46:56.092 \rightarrow 00:46:58.360$ I'm trying to see if I can study

NOTE Confidence: 0.44133765

 $00:46:58.360 \rightarrow 00:47:00.360$ pain and suicidality simultaneously,

NOTE Confidence: 0.44133765

 $00:47:00.360 \longrightarrow 00:47:01.491$ 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
- $00{:}47{:}04.688 \dashrightarrow 00{:}47{:}07.220$ 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
- $00{:}47{:}12.741 \dashrightarrow 00{:}47{:}14.460$ cannabis as compared to people
- NOTE Confidence: 0.44133765
- $00{:}47{:}14.460 \dashrightarrow 00{:}47{:}16.035$ who do not use cannabis.
- NOTE Confidence: 0.44133765
- $00:47:16.040 \longrightarrow 00:47:17.432$ And I know a lot of people use
- NOTE Confidence: 0.44133765
- $00{:}47{:}17{.}432 \dashrightarrow 00{:}47{:}18{.}718$ cannabis and report using cannabis.
- NOTE Confidence: 0.44133765
- $00{:}47{:}18.720 \dashrightarrow 00{:}47{:}22.960$ And again, this is across stress groups.
- NOTE Confidence: 0.44133765
- $00:47:22.960 \longrightarrow 00:47:24.612$ People call us and they say they
- NOTE Confidence: 0.44133765
- $00:47:24.612 \longrightarrow 00:47:26.018$ use cannabis to relieve their
- NOTE Confidence: 0.44133765
- $00{:}47{:}26.018 \dashrightarrow 00{:}47{:}27.618$ PTSD symptoms or their anxiety
- NOTE Confidence: 0.44133765
- $00:47:27.618 \rightarrow 00:47:29.080$ symptoms or whatever symptoms,
- NOTE Confidence: 0.44133765
- $00{:}47{:}29{.}080 \dashrightarrow 00{:}47{:}30{.}223$ their pain symptoms.
- NOTE Confidence: 0.44133765
- $00{:}47{:}30{.}223 \dashrightarrow 00{:}47{:}32{.}890$ But it appears that use of cannabis
- NOTE Confidence: 0.44133765

 $00{:}47{:}32.964 \dashrightarrow 00{:}47{:}35.280$ is actually up regulating MGULA 5,

NOTE Confidence: 0.44133765

 $00{:}47{:}35{.}280 \dashrightarrow 00{:}47{:}36{.}875$ which may potentially put these

NOTE Confidence: 0.44133765

 $00:47:36.875 \rightarrow 00:47:39.200$ 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

 $00{:}47{:}40{.}840 \dashrightarrow 00{:}47{:}43{.}817$ it's all preliminary data that

NOTE Confidence: 0.44133765

 $00{:}47{:}43.817 \dashrightarrow 00{:}47{:}45.359$ we we're playing around with to

NOTE Confidence: 0.44133765

 $00:47:45.359 \longrightarrow 00:47:47.039$ 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

 $00{:}47{:}48.906 \dashrightarrow 00{:}47{:}50.488$ together to collaborate, let me know.

NOTE Confidence: 0.44133765

 $00{:}47{:}50{.}488 \dashrightarrow 00{:}47{:}52{.}560$ And thank you so much for your attention.

NOTE Confidence: 0.32573488

 $00{:}47{:}59.560 \dashrightarrow 00{:}48{:}00.280$ Thanks, Irena.