

WEBVTT

NOTE duration:"00:48:45"

NOTE recognizability:0.810

NOTE language:en-us

NOTE Confidence: 0.9115704

00:00:00.000 --> 00:00:03.680 Well. Thank you so much Jerry

NOTE Confidence: 0.9115704

00:00:03.680 --> 00:00:05.144 for the kind introduction.

NOTE Confidence: 0.9115704

00:00:05.150 --> 00:00:07.290 It's truly a pleasure and

NOTE Confidence: 0.9115704

00:00:07.290 --> 00:00:09.430 honor to give this lecture.

NOTE Confidence: 0.9115704

00:00:09.430 --> 00:00:12.662 I was there last time at Yale in 2009.

NOTE Confidence: 0.9115704

00:00:12.662 --> 00:00:15.406 I I met Doctor Henninger back then

NOTE Confidence: 0.9115704

00:00:15.406 --> 00:00:19.010 but I know of all many of the stories.

NOTE Confidence: 0.9115704

00:00:19.010 --> 00:00:22.946 Wonderful teacher, mentor,

NOTE Confidence: 0.9115704

00:00:22.946 --> 00:00:25.570 researcher, clinician.

NOTE Confidence: 0.9115704

00:00:25.570 --> 00:00:27.964 And we share a story where he

NOTE Confidence: 0.9115704

00:00:27.964 --> 00:00:30.013 sounds like his second generation

NOTE Confidence: 0.9115704

00:00:30.013 --> 00:00:32.839 psychiatrist grew up and they a

NOTE Confidence: 0.9115704

00:00:32.839 --> 00:00:35.160 mental state hospital grounds.

NOTE Confidence: 0.9115704

00:00:35.160 --> 00:00:38.960 I also second generation psychiatrist,

NOTE Confidence: 0.9115704

00:00:38.960 --> 00:00:41.420 and I grew up on Norristown

NOTE Confidence: 0.9115704

00:00:41.420 --> 00:00:43.000 State Hospital grounds that we

NOTE Confidence: 0.9115704

00:00:43.000 --> 00:00:44.974 used to play there because my

NOTE Confidence: 0.9115704

00:00:44.974 --> 00:00:46.639 father was working at Norristown,

NOTE Confidence: 0.9115704

00:00:46.640 --> 00:00:49.024 we lived on Sturgis St and I think

NOTE Confidence: 0.9115704

00:00:49.024 --> 00:00:50.860 George Curtis was there and some

NOTE Confidence: 0.9115704

00:00:50.860 --> 00:00:53.288 of the earlier trials of lithium

NOTE Confidence: 0.9115704

00:00:53.288 --> 00:00:56.384 with Smith Beecham if I recall.

NOTE Confidence: 0.9115704

00:00:56.390 --> 00:00:59.086 And we used to play with our with

NOTE Confidence: 0.9115704

00:00:59.086 --> 00:01:01.434 with patients there who had the

NOTE Confidence: 0.9115704

00:01:01.434 --> 00:01:03.429 transistor radios and they would

NOTE Confidence: 0.9115704

00:01:03.430 --> 00:01:05.390 provide moral therapy and and

NOTE Confidence: 0.9115704

00:01:05.390 --> 00:01:08.190 educate them on how to socialize.

NOTE Confidence: 0.9115704

00:01:08.190 --> 00:01:12.636 So we have that common experience.

NOTE Confidence: 0.9115704

00:01:12.640 --> 00:01:14.944 So with that in mind, I'm I'm,

NOTE Confidence: 0.9115704
00:01:14.944 --> 00:01:15.448 you know,
NOTE Confidence: 0.9115704
00:01:15.448 --> 00:01:17.270 truly delighted to to give this talk,
NOTE Confidence: 0.9115704
00:01:17.270 --> 00:01:18.560 I'm going to probably have way
NOTE Confidence: 0.9115704
00:01:18.560 --> 00:01:19.205 too many slides.
NOTE Confidence: 0.858486836
00:01:21.400 --> 00:01:23.730 And just wanted to summarize
NOTE Confidence: 0.858486836
00:01:23.730 --> 00:01:26.060 the work until this point.
NOTE Confidence: 0.858486836
00:01:26.060 --> 00:01:28.930 This is my disclosure work for the
NOTE Confidence: 0.858486836
00:01:28.930 --> 00:01:30.689 intramural research program at NIH.
NOTE Confidence: 0.858486836
00:01:30.690 --> 00:01:33.588 So today's objectives are to understand
NOTE Confidence: 0.858486836
00:01:33.588 --> 00:01:37.049 briefly the cause of TRD to become
NOTE Confidence: 0.858486836
00:01:37.049 --> 00:01:39.464 familiar with rapid actin therapeutics
NOTE Confidence: 0.858486836
00:01:39.464 --> 00:01:41.970 for TRD to understand the neurobiology
NOTE Confidence: 0.858486836
00:01:41.970 --> 00:01:44.280 of promise and therapeutics for treatment
NOTE Confidence: 0.858486836
00:01:44.339 --> 00:01:47.234 resistant depression and to really get
NOTE Confidence: 0.858486836
00:01:47.234 --> 00:01:49.514 at the pharmacology understanding how
NOTE Confidence: 0.858486836

00:01:49.514 --> 00:01:52.539 ketamine works to develop better treatments.
NOTE Confidence: 0.858486836

00:01:52.540 --> 00:01:55.879 So we do know already that TRD is associated
NOTE Confidence: 0.858486836

00:01:55.879 --> 00:01:58.595 with is a major cause of morbidity,
NOTE Confidence: 0.858486836

00:01:58.600 --> 00:02:00.886 disability and mortality,
NOTE Confidence: 0.858486836

00:02:00.886 --> 00:02:06.210 and it's defined clinically by two failure to
NOTE Confidence: 0.858486836

00:02:06.210 --> 00:02:08.460 respond to two adequate antidepressant trials
NOTE Confidence: 0.858486836

00:02:08.460 --> 00:02:11.238 in the current major depressive episode.
NOTE Confidence: 0.858486836

00:02:11.240 --> 00:02:14.279 It's made about 30 to 40% will have some
NOTE Confidence: 0.858486836

00:02:14.279 --> 00:02:15.944 form of treatment resistant depression,
NOTE Confidence: 0.858486836

00:02:15.950 --> 00:02:18.032 although the numbers are probably actually
NOTE Confidence: 0.858486836

00:02:18.032 --> 00:02:19.780 higher and depression, as you know,
NOTE Confidence: 0.858486836

00:02:19.780 --> 00:02:23.270 is associated with significant mortality.
NOTE Confidence: 0.858486836

00:02:23.270 --> 00:02:26.350 Death by suicide is about 800,000 to
NOTE Confidence: 0.858486836

00:02:26.350 --> 00:02:28.720 1,000,000 per year around the world.
NOTE Confidence: 0.858486836

00:02:28.720 --> 00:02:30.148 Depression has traditionally been
NOTE Confidence: 0.858486836

00:02:30.148 --> 00:02:31.933 viewed as disturbances of mood,

NOTE Confidence: 0.858486836
00:02:31.940 --> 00:02:34.138 but we know it consists of much
NOTE Confidence: 0.858486836
00:02:34.138 --> 00:02:35.080 more than that.
NOTE Confidence: 0.858486836
00:02:35.080 --> 00:02:35.604 Disturbances,
NOTE Confidence: 0.858486836
00:02:35.604 --> 00:02:36.652 circadian rhythms,
NOTE Confidence: 0.858486836
00:02:36.652 --> 00:02:38.224 activity levels with
NOTE Confidence: 0.858486836
00:02:38.224 --> 00:02:39.796 significant impairment function,
NOTE Confidence: 0.858486836
00:02:39.800 --> 00:02:42.938 and there's considerable cost with a
NOTE Confidence: 0.858486836
00:02:42.938 --> 00:02:45.734 treatment resistant depression and the if
NOTE Confidence: 0.858486836
00:02:45.734 --> 00:02:47.774 you have treatment resistant depression,
NOTE Confidence: 0.858486836
00:02:47.780 --> 00:02:49.838 you live on average 13 years less
NOTE Confidence: 0.858486836
00:02:49.838 --> 00:02:51.260 than individuals without treatment
NOTE Confidence: 0.858486836
00:02:51.260 --> 00:02:52.240 persist depression,
NOTE Confidence: 0.858486836
00:02:52.240 --> 00:02:55.640 so really impactful illness.
NOTE Confidence: 0.858486836
00:02:55.640 --> 00:02:58.144 The the criteria for DSM we we we
NOTE Confidence: 0.858486836
00:02:58.144 --> 00:03:00.441 have DSM criteria for depression
NOTE Confidence: 0.858486836

00:03:00.441 --> 00:03:03.091 and it's useful for communicating
NOTE Confidence: 0.858486836

00:03:03.091 --> 00:03:05.718 with families and with clinicians.
NOTE Confidence: 0.858486836

00:03:05.720 --> 00:03:07.946 But we know that it does not
NOTE Confidence: 0.858486836

00:03:07.946 --> 00:03:08.900 map to neurobiology.
NOTE Confidence: 0.858486836

00:03:08.900 --> 00:03:11.120 In fact there is conservative
NOTE Confidence: 0.858486836

00:03:11.120 --> 00:03:14.228 comorbidity of 30 to 40% or even higher,
NOTE Confidence: 0.858486836

00:03:14.228 --> 00:03:16.913 and so if one is trying to understand
NOTE Confidence: 0.858486836

00:03:16.913 --> 00:03:19.057 the ideology of depression,
NOTE Confidence: 0.858486836

00:03:19.060 --> 00:03:21.340 are you really looking at
NOTE Confidence: 0.858486836

00:03:21.340 --> 00:03:23.620 depression or the comorbidity with
NOTE Confidence: 0.858486836

00:03:23.704 --> 00:03:26.139 anxiety disorders or some other?
NOTE Confidence: 0.858486836

00:03:26.140 --> 00:03:28.775 Medical conditions and So what
NOTE Confidence: 0.858486836

00:03:28.775 --> 00:03:31.566 was proposed with our DOC research
NOTE Confidence: 0.858486836

00:03:31.566 --> 00:03:33.302 domain criteria was deconstruct
NOTE Confidence: 0.858486836

00:03:33.302 --> 00:03:35.459 these illness illnesses into more
NOTE Confidence: 0.858486836

00:03:35.459 --> 00:03:37.484 simpler constructs in the way,

NOTE Confidence: 0.858486836

00:03:37.490 --> 00:03:38.942 but challenge in itself.

NOTE Confidence: 0.858486836

00:03:38.942 --> 00:03:42.033 And here we have example of an adonia

NOTE Confidence: 0.858486836

00:03:42.033 --> 00:03:44.547 motoric or activity levels in suicide,

NOTE Confidence: 0.858486836

00:03:44.550 --> 00:03:46.974 and so then what you do is obtain

NOTE Confidence: 0.858486836

00:03:46.974 --> 00:03:48.909 information at very various levels,

NOTE Confidence: 0.858486836

00:03:48.910 --> 00:03:51.010 going from behavior going through

NOTE Confidence: 0.858486836

00:03:51.010 --> 00:03:53.110 Physiology circuits all the way

NOTE Confidence: 0.858486836

00:03:53.174 --> 00:03:55.382 down to genes and then especially

NOTE Confidence: 0.858486836

00:03:55.382 --> 00:03:57.180 and then eventually you can.

NOTE Confidence: 0.858486836

00:03:57.180 --> 00:03:59.550 Link and the phenotype more closely

NOTE Confidence: 0.858486836

00:03:59.550 --> 00:04:01.854 or approximate to what's going on

NOTE Confidence: 0.858486836

00:04:01.854 --> 00:04:03.828 with the ideology of the illness

NOTE Confidence: 0.858486836

00:04:03.828 --> 00:04:06.198 with the therapeutic in this case.

NOTE Confidence: 0.858486836

00:04:06.200 --> 00:04:07.400 For example,

NOTE Confidence: 0.858486836

00:04:07.400 --> 00:04:10.400 this represents changes in anhedonia,

NOTE Confidence: 0.858486836

00:04:10.400 --> 00:04:13.080 reward processing link with improvements
NOTE Confidence: 0.858486836

00:04:13.080 --> 00:04:15.760 and depression scores with ketamine,
NOTE Confidence: 0.858486836

00:04:15.760 --> 00:04:17.936 and that would be one example of how
NOTE Confidence: 0.858486836

00:04:17.936 --> 00:04:20.320 we can develop better therapeutics.
NOTE Confidence: 0.858486836

00:04:20.320 --> 00:04:20.609 Now,
NOTE Confidence: 0.858486836

00:04:20.609 --> 00:04:22.632 the rationale is that you know depression
NOTE Confidence: 0.858486836

00:04:22.632 --> 00:04:24.858 is for developing better treatments.
NOTE Confidence: 0.858486836

00:04:24.860 --> 00:04:26.470 As we have depressions associated
NOTE Confidence: 0.858486836

00:04:26.470 --> 00:04:28.080 with the disruption to personal,
NOTE Confidence: 0.858486836

00:04:28.080 --> 00:04:28.516 social,
NOTE Confidence: 0.858486836

00:04:28.516 --> 00:04:30.696 occupational life and there's a
NOTE Confidence: 0.858486836

00:04:30.696 --> 00:04:32.440 considerable risk of suicide.
NOTE Confidence: 0.858486836

00:04:32.440 --> 00:04:34.380 Although we have standard treatments,
NOTE Confidence: 0.858486836

00:04:34.380 --> 00:04:35.610 psychosocial, pharmacological,
NOTE Confidence: 0.858486836

00:04:35.610 --> 00:04:36.225 neurostimulation,
NOTE Confidence: 0.858486836

00:04:36.225 --> 00:04:39.915 they all help many individuals oppression.

NOTE Confidence: 0.858486836
00:04:39.920 --> 00:04:41.140 We use them in combination,
NOTE Confidence: 0.858486836
00:04:41.140 --> 00:04:44.556 but still Despite that we get very
NOTE Confidence: 0.858486836
00:04:44.556 --> 00:04:46.020 low remission rates.
NOTE Confidence: 0.858486836
00:04:46.020 --> 00:04:49.496 We have about 30 to 40% of treatment
NOTE Confidence: 0.858486836
00:04:49.496 --> 00:04:50.332 resistant depression.
NOTE Confidence: 0.858486836
00:04:50.332 --> 00:04:52.840 And there's a considerable lag of
NOTE Confidence: 0.858486836
00:04:52.902 --> 00:04:54.870 onset of antidepressant effects.
NOTE Confidence: 0.858216380555556
00:04:54.870 --> 00:04:57.408 This cartoon or this figure depicts
NOTE Confidence: 0.858216380555556
00:04:57.408 --> 00:04:59.511 a major depressive episode which
NOTE Confidence: 0.858216380555556
00:04:59.511 --> 00:05:01.898 usually lasts about 6 to 9 months.
NOTE Confidence: 0.858216380555556
00:05:01.900 --> 00:05:04.000 What happens when we initiate treatment
NOTE Confidence: 0.858216380555556
00:05:04.000 --> 00:05:06.250 with a monoaminergic based antidepressant?
NOTE Confidence: 0.858216380555556
00:05:06.250 --> 00:05:07.858 Is we shift the curve of
NOTE Confidence: 0.858216380555556
00:05:07.858 --> 00:05:08.930 response towards the left,
NOTE Confidence: 0.858216380555556
00:05:08.930 --> 00:05:12.970 and that response is now at 10 to 14 weeks.
NOTE Confidence: 0.858216380555556

00:05:12.970 --> 00:05:16.006 Now, in my mind and many,
NOTE Confidence: 0.858216380555556

00:05:16.010 --> 00:05:19.030 we would agree that next
NOTE Confidence: 0.858216380555556

00:05:19.030 --> 00:05:20.238 generation antidepressants.
NOTE Confidence: 0.858216380555556

00:05:20.240 --> 00:05:22.620 That could produce rapid responses
NOTE Confidence: 0.858216380555556

00:05:22.620 --> 00:05:25.000 of both depression and suicide
NOTE Confidence: 0.858216380555556

00:05:25.078 --> 00:05:26.908 within a matter of hours,
NOTE Confidence: 0.858216380555556

00:05:26.910 --> 00:05:29.214 and we can develop better treatments
NOTE Confidence: 0.858216380555556

00:05:29.214 --> 00:05:31.846 than ketamine based on an understanding
NOTE Confidence: 0.858216380555556

00:05:31.846 --> 00:05:33.890 of cellular molecular targets.
NOTE Confidence: 0.858216380555556

00:05:33.890 --> 00:05:38.794 Now this is, yes, you know this,
NOTE Confidence: 0.858216380555556

00:05:38.794 --> 00:05:40.810 the path or the journey to novel
NOTE Confidence: 0.858216380555556

00:05:40.876 --> 00:05:42.200 therapeutics was made much
NOTE Confidence: 0.858216380555556

00:05:42.200 --> 00:05:44.186 easier by the work at Yale,
NOTE Confidence: 0.858216380555556

00:05:44.190 --> 00:05:48.366 and this is the Seminole paper by Rob Berman,
NOTE Confidence: 0.858216380555556

00:05:48.366 --> 00:05:50.262 John Crystal, Dennis, Charney,
NOTE Confidence: 0.858216380555556

00:05:50.262 --> 00:05:52.122 and others showing the rapid

NOTE Confidence: 0.858216380555556
00:05:52.122 --> 00:05:54.210 response within a couple of hours.
NOTE Confidence: 0.858216380555556
00:05:54.210 --> 00:05:56.814 And it really set the the the
NOTE Confidence: 0.858216380555556
00:05:56.814 --> 00:05:58.999 groundwork for future research at
NOTE Confidence: 0.858216380555556
00:05:58.999 --> 00:06:01.410 the intramural program this work.
NOTE Confidence: 0.858216380555556
00:06:01.410 --> 00:06:04.170 This is a very old slide.
NOTE Confidence: 0.858216380555556
00:06:04.170 --> 00:06:06.840 From a paper where we had
NOTE Confidence: 0.858216380555556
00:06:06.840 --> 00:06:08.175 our candidate drugs,
NOTE Confidence: 0.858216380555556
00:06:08.180 --> 00:06:11.006 this was our understanding of the
NOTE Confidence: 0.858216380555556
00:06:11.006 --> 00:06:13.490 architecture of the glutamate system,
NOTE Confidence: 0.858216380555556
00:06:13.490 --> 00:06:14.477 the tripartite system,
NOTE Confidence: 0.858216380555556
00:06:14.477 --> 00:06:16.780 and we came up over the few
NOTE Confidence: 0.858216380555556
00:06:16.849 --> 00:06:18.636 drugs and amantine, felbamate,
NOTE Confidence: 0.858216380555556
00:06:18.636 --> 00:06:20.244 riluzole early on,
NOTE Confidence: 0.858216380555556
00:06:20.244 --> 00:06:22.924 and I'll very briefly summarize
NOTE Confidence: 0.858216380555556
00:06:22.924 --> 00:06:24.459 the next steps,
NOTE Confidence: 0.858216380555556

00:06:24.460 --> 00:06:27.106 but that we've gone through 20 years
NOTE Confidence: 0.858216380555556

00:06:27.106 --> 00:06:29.683 of different drugs and some of them
NOTE Confidence: 0.858216380555556

00:06:29.683 --> 00:06:31.741 have promised and others did not.
NOTE Confidence: 0.858216380555556

00:06:31.750 --> 00:06:35.534 But this is the the study that Jerry
NOTE Confidence: 0.858216380555556

00:06:35.534 --> 00:06:37.950 mentioned where we tested back then.
NOTE Confidence: 0.858216380555556

00:06:37.950 --> 00:06:41.270 But we we believe was the NMDA receptor
NOTE Confidence: 0.858216380555556

00:06:41.270 --> 00:06:43.130 inhibition hypothesis of depression.
NOTE Confidence: 0.858216380555556

00:06:43.130 --> 00:06:45.586 That is, if you're given an MD antagonist,
NOTE Confidence: 0.858216380555556

00:06:45.590 --> 00:06:47.418 you produce rapid responses
NOTE Confidence: 0.858216380555556

00:06:47.418 --> 00:06:49.703 and the answer is yes.
NOTE Confidence: 0.858216380555556

00:06:49.710 --> 00:06:52.210 Here we see racemic, ketamine,
NOTE Confidence: 0.858216380555556

00:06:52.210 --> 00:06:53.350 the depression scores,
NOTE Confidence: 0.858216380555556

00:06:53.350 --> 00:06:54.110 higher number,
NOTE Confidence: 0.858216380555556

00:06:54.110 --> 00:06:56.798 greater depression time and minutes and days,
NOTE Confidence: 0.858216380555556

00:06:56.800 --> 00:06:58.613 and we see an onset within a
NOTE Confidence: 0.858216380555556

00:06:58.613 --> 00:07:00.244 couple of hours with racemic

NOTE Confidence: 0.858216380555556
00:07:00.244 --> 00:07:01.816 ketamine towards the right.
NOTE Confidence: 0.858216380555556
00:07:01.820 --> 00:07:04.562 We see the response rates of
NOTE Confidence: 0.858216380555556
00:07:04.562 --> 00:07:05.933 monomer energetic antidepressants,
NOTE Confidence: 0.858216380555556
00:07:05.940 --> 00:07:10.298 which is about 6 to 8 weeks for 65%
NOTE Confidence: 0.858216380555556
00:07:10.298 --> 00:07:12.446 to achieve response taken and added
NOTE Confidence: 0.858216380555556
00:07:12.446 --> 00:07:14.777 present everyday for that period of time.
NOTE Confidence: 0.858216380555556
00:07:14.780 --> 00:07:16.982 Here you see rapid responses within
NOTE Confidence: 0.858216380555556
00:07:16.982 --> 00:07:19.749 a couple of hours in individuals who
NOTE Confidence: 0.858216380555556
00:07:19.749 --> 00:07:22.197 had failed 6 to 8 antidepressants,
NOTE Confidence: 0.858216380555556
00:07:22.200 --> 00:07:25.056 many had failed ECT and 50%
NOTE Confidence: 0.858216380555556
00:07:25.060 --> 00:07:29.648 had previous suicide attempts.
NOTE Confidence: 0.858216380555556
00:07:29.650 --> 00:07:31.440 So.
NOTE Confidence: 0.858216380555556
00:07:31.440 --> 00:07:33.946 From there we now have what could
NOTE Confidence: 0.858216380555556
00:07:33.946 --> 00:07:36.073 be called four major classes
NOTE Confidence: 0.858216380555556
00:07:36.073 --> 00:07:38.983 of of drugs that have presumed
NOTE Confidence: 0.858216380555556

00:07:38.983 --> 00:07:40.560 rapid antidepressant effect.
NOTE Confidence: 0.858216380555556

00:07:40.560 --> 00:07:43.386 We have ketamine as the prototype
NOTE Confidence: 0.858216380555556

00:07:43.386 --> 00:07:44.799 and the antagonist,
NOTE Confidence: 0.858216380555556

00:07:44.800 --> 00:07:46.900 but also has effects on new
NOTE Confidence: 0.858216380555556

00:07:46.900 --> 00:07:48.940 opioid Kappa and other systems.
NOTE Confidence: 0.858216380555556

00:07:48.940 --> 00:07:51.510 The second group is neurosteroids
NOTE Confidence: 0.858216380555556

00:07:51.510 --> 00:07:52.950 brexanolone sage 547.
NOTE Confidence: 0.858216380555556

00:07:52.950 --> 00:07:54.180 It's a gab.
NOTE Confidence: 0.858216380555556

00:07:54.180 --> 00:07:57.580 It's a GABA a positive electric modulator.
NOTE Confidence: 0.858216380555556

00:07:57.580 --> 00:08:00.828 Then we have the opioids and then
NOTE Confidence: 0.858216380555556

00:08:00.828 --> 00:08:01.756 serotonergic hallucinogens.
NOTE Confidence: 0.858216380555556

00:08:01.760 --> 00:08:03.804 The prototype is silybin.
NOTE Confidence: 0.858216380555556

00:08:03.804 --> 00:08:06.359 Now we're really not sure,
NOTE Confidence: 0.858216380555556

00:08:06.360 --> 00:08:08.790 but early preclinical work suggests
NOTE Confidence: 0.858216380555556

00:08:08.790 --> 00:08:11.652 that there's overlaps in some of
NOTE Confidence: 0.858216380555556

00:08:11.652 --> 00:08:14.137 the the the effects of these drugs,

NOTE Confidence: 0.858216380555556

00:08:14.140 --> 00:08:16.240 so they begin at the receptor

NOTE Confidence: 0.858216380555556

00:08:16.240 --> 00:08:16.940 signaling level.

NOTE Confidence: 0.858216380555556

00:08:16.940 --> 00:08:18.020 Different places,

NOTE Confidence: 0.858216380555556

00:08:18.020 --> 00:08:19.640 opioid and MDA,

NOTE Confidence: 0.858216380555556

00:08:19.640 --> 00:08:20.912 glutamate or serotonergic,

NOTE Confidence: 0.858216380555556

00:08:20.912 --> 00:08:23.456 then and then we see differences

NOTE Confidence: 0.858216380555556

00:08:23.456 --> 00:08:25.704 in the plasticity cascades and

NOTE Confidence: 0.858216380555556

00:08:25.704 --> 00:08:27.894 more downstream that was believed

NOTE Confidence: 0.858216380555556

00:08:27.894 --> 00:08:31.316 to happen is that they overlap at

NOTE Confidence: 0.858216380555556

00:08:31.316 --> 00:08:32.774 network reconfiguration increase.

NOTE Confidence: 0.62119054

00:08:32.780 --> 00:08:34.884 The Neurotrophins protein translation.

NOTE Confidence: 0.62119054

00:08:34.884 --> 00:08:36.450 Spine turnover, neurogenesis,

NOTE Confidence: 0.62119054

00:08:36.450 --> 00:08:40.020 and these different systems seem to converge,

NOTE Confidence: 0.62119054

00:08:40.020 --> 00:08:42.070 and glutamate seems to be

NOTE Confidence: 0.62119054

00:08:42.070 --> 00:08:43.615 an important component now.

NOTE Confidence: 0.62119054

00:08:43.615 --> 00:08:46.135 There have been studies with this earth with
NOTE Confidence: 0.62119054

00:08:46.135 --> 00:08:48.767 the psychedelic agents and this was where,
NOTE Confidence: 0.62119054

00:08:48.770 --> 00:08:51.158 by Robin Carhartt Harris just published
NOTE Confidence: 0.62119054

00:08:51.158 --> 00:08:53.900 recently in the New England Journal,
NOTE Confidence: 0.62119054

00:08:53.900 --> 00:08:55.868 in which you see,
NOTE Confidence: 0.62119054

00:08:55.868 --> 00:08:58.820 here is subjects randomized to silybin.
NOTE Confidence: 0.62119054

00:08:58.820 --> 00:09:01.976 2 doses of citalopram and what
NOTE Confidence: 0.62119054

00:09:01.976 --> 00:09:04.590 you see here is the conclusion,
NOTE Confidence: 0.62119054

00:09:04.590 --> 00:09:05.865 at least on the quiz.
NOTE Confidence: 0.62119054

00:09:05.870 --> 00:09:08.246 Was that there was at by six weeks there
NOTE Confidence: 0.62119054

00:09:08.246 --> 00:09:10.770 was no significant difference in the end
NOTE Confidence: 0.62119054

00:09:10.770 --> 00:09:13.079 of person effects versus search ruling
NOTE Confidence: 0.62119054

00:09:13.080 --> 00:09:16.440 compass just published a larger study.
NOTE Confidence: 0.62119054

00:09:16.440 --> 00:09:19.020 Looking at, I believe it was
NOTE Confidence: 0.62119054

00:09:19.020 --> 00:09:22.390 2510 milligrams and 1 milligram.
NOTE Confidence: 0.62119054

00:09:22.390 --> 00:09:25.614 And what they found were response rates of

NOTE Confidence: 0.62119054

00:09:25.614 --> 00:09:28.645 about 36% at 25 milligrams at three weeks.

NOTE Confidence: 0.62119054

00:09:28.650 --> 00:09:30.816 And then there's some cases of,

NOTE Confidence: 0.62119054

00:09:30.820 --> 00:09:31.826 you know,

NOTE Confidence: 0.62119054

00:09:31.826 --> 00:09:34.214 perhaps increased rates of suicidal

NOTE Confidence: 0.62119054

00:09:34.214 --> 00:09:36.832 ideation and so on and so forth

NOTE Confidence: 0.62119054

00:09:36.832 --> 00:09:39.650 and in in the higher dose group.

NOTE Confidence: 0.62119054

00:09:39.650 --> 00:09:41.700 But these are just preliminary.

NOTE Confidence: 0.62119054

00:09:41.700 --> 00:09:43.968 The results are not all published,

NOTE Confidence: 0.62119054

00:09:43.970 --> 00:09:46.064 but leads us to believe that

NOTE Confidence: 0.62119054

00:09:46.064 --> 00:09:47.909 this could possibly be another

NOTE Confidence: 0.62119054

00:09:47.909 --> 00:09:50.609 group of drugs to to pursue.

NOTE Confidence: 0.62119054

00:09:50.609 --> 00:09:53.747 This is very high level summary.

NOTE Confidence: 0.62119054

00:09:53.750 --> 00:09:57.215 This is the Ron Duman hypothesis of

NOTE Confidence: 0.62119054

00:09:57.215 --> 00:09:59.825 depression, the glutamatergic burst,

NOTE Confidence: 0.62119054

00:09:59.825 --> 00:10:03.638 where we block GABA NMDA receptors

NOTE Confidence: 0.62119054

00:10:03.638 --> 00:10:06.108 and GABA ergic interneurons decreased.
NOTE Confidence: 0.62119054

00:10:06.110 --> 00:10:07.750 GABA release hyperpolarization and
NOTE Confidence: 0.62119054

00:10:07.750 --> 00:10:09.978 the so called glutamate, first,
NOTE Confidence: 0.62119054

00:10:09.978 --> 00:10:11.742 intracellular signaling cascade
NOTE Confidence: 0.62119054

00:10:11.742 --> 00:10:14.682 changes induction of neural plasticity,
NOTE Confidence: 0.62119054

00:10:14.690 --> 00:10:18.290 and then spine growth in synaptogenesis.
NOTE Confidence: 0.62119054

00:10:18.290 --> 00:10:20.108 Another possibility is to go more
NOTE Confidence: 0.62119054

00:10:20.108 --> 00:10:21.900 downstream to avoid NMDA receptors,
NOTE Confidence: 0.62119054

00:10:21.900 --> 00:10:22.974 and hopefully.
NOTE Confidence: 0.62119054

00:10:22.974 --> 00:10:26.196 Avoid the psychotomimetic effects would be
NOTE Confidence: 0.62119054

00:10:26.196 --> 00:10:29.238 using inhibitors that maglore to receptors.
NOTE Confidence: 0.62119054

00:10:29.240 --> 00:10:31.053 One can look at the son of
NOTE Confidence: 0.62119054

00:10:31.053 --> 00:10:32.519 ketamine to our six rhink.
NOTE Confidence: 0.62119054

00:10:32.520 --> 00:10:33.955 I'll talk a little bit about that.
NOTE Confidence: 0.62119054

00:10:33.960 --> 00:10:36.885 They all produce the glutamate
NOTE Confidence: 0.62119054

00:10:36.885 --> 00:10:38.640 burst AMPA activation,

NOTE Confidence: 0.62119054

00:10:38.640 --> 00:10:39.080 serotonergic,

NOTE Confidence: 0.62119054

00:10:39.080 --> 00:10:41.720 psychedelics at the five HT 2A

NOTE Confidence: 0.62119054

00:10:41.720 --> 00:10:44.440 receptor and also would have many

NOTE Confidence: 0.62119054

00:10:44.440 --> 00:10:46.655 of the common downstream pathways.

NOTE Confidence: 0.62119054

00:10:46.660 --> 00:10:49.872 We do not know about the neurosteroids

NOTE Confidence: 0.62119054

00:10:49.872 --> 00:10:52.948 we do know that there's.

NOTE Confidence: 0.62119054

00:10:52.948 --> 00:10:55.380 They're positive, illustrate modulators.

NOTE Confidence: 0.62119054

00:10:55.380 --> 00:10:57.312 Some argue it could be negative

NOTE Confidence: 0.62119054

00:10:57.312 --> 00:10:57.956 allosteric modulators,

NOTE Confidence: 0.62119054

00:10:57.960 --> 00:11:01.280 but they seem to tap in and similar

NOTE Confidence: 0.62119054

00:11:01.280 --> 00:11:03.019 downstream pathways early work.

NOTE Confidence: 0.62119054

00:11:03.020 --> 00:11:05.180 Now, what is important in and,

NOTE Confidence: 0.62119054

00:11:05.180 --> 00:11:09.080 and this is that biomarkers where this

NOTE Confidence: 0.62119054

00:11:09.080 --> 00:11:11.640 inhibition disinhibition or excitation

NOTE Confidence: 0.62119054

00:11:11.640 --> 00:11:17.748 of pyramidal cells one can detect.

NOTE Confidence: 0.62119054

00:11:17.750 --> 00:11:20.347 At the preclinical and also human level,
NOTE Confidence: 0.62119054

00:11:20.350 --> 00:11:21.790 looking at gamma power within
NOTE Confidence: 0.62119054

00:11:21.790 --> 00:11:23.230 the 30 to 50 Hertz,
NOTE Confidence: 0.62119054

00:11:23.230 --> 00:11:25.918 and that is a potential cross
NOTE Confidence: 0.62119054

00:11:25.918 --> 00:11:28.550 species biomarker we are pursuing.
NOTE Confidence: 0.62119054

00:11:28.550 --> 00:11:31.589 So this is a very simple schematic in the
NOTE Confidence: 0.62119054

00:11:31.589 --> 00:11:35.290 year 2000 and this is what it looks like now.
NOTE Confidence: 0.62119054

00:11:35.290 --> 00:11:36.598 Very exciting,
NOTE Confidence: 0.62119054

00:11:36.598 --> 00:11:39.868 many different targets being pursued,
NOTE Confidence: 0.62119054

00:11:39.870 --> 00:11:40.970 some of them panned out,
NOTE Confidence: 0.62119054

00:11:40.970 --> 00:11:41.990 others not.
NOTE Confidence: 0.62119054

00:11:41.990 --> 00:11:45.050 We talked about the Gabaergic interneurons
NOTE Confidence: 0.62119054

00:11:45.050 --> 00:11:47.720 and blue are two three ketamine.
NOTE Confidence: 0.62119054

00:11:47.720 --> 00:11:50.780 Seems to have effects on many
NOTE Confidence: 0.62119054

00:11:50.780 --> 00:11:51.800 different components.
NOTE Confidence: 0.62119054

00:11:51.800 --> 00:11:55.634 The Mglur 5 has also been pursued as well.

NOTE Confidence: 0.62119054

00:11:55.640 --> 00:11:57.860 Colocalized within MDA receptors.

NOTE Confidence: 0.62119054

00:11:57.860 --> 00:12:01.292 Some have actually pursued more activators.

NOTE Confidence: 0.62119054

00:12:01.292 --> 00:12:05.204 Tax 653 is still in play.

NOTE Confidence: 0.62119054

00:12:05.210 --> 00:12:09.416 Also for neurocognition one can target

NOTE Confidence: 0.62119054

00:12:09.416 --> 00:12:12.220 the extrasynaptic site receptors

NOTE Confidence: 0.62119054

00:12:12.220 --> 00:12:16.100 to produce this a plasticity.

NOTE Confidence: 0.62119054

00:12:16.100 --> 00:12:18.110 But and then of course.

NOTE Confidence: 0.62119054

00:12:18.110 --> 00:12:20.290 There are more direct targets

NOTE Confidence: 0.62119054

00:12:20.290 --> 00:12:22.034 such as mtor agonists,

NOTE Confidence: 0.852174034285714

00:12:22.040 --> 00:12:25.554 MV5138. Now the largest group of drugs,

NOTE Confidence: 0.852174034285714

00:12:25.560 --> 00:12:28.395 of course, are the NMDA receptor antagonist,

NOTE Confidence: 0.852174034285714

00:12:28.400 --> 00:12:30.338 and so there are listed here.

NOTE Confidence: 0.852174034285714

00:12:30.340 --> 00:12:33.328 One that's quite interested as dextral

NOTE Confidence: 0.852174034285714

00:12:33.328 --> 00:12:36.644 methadone rail 1017 and then one can

NOTE Confidence: 0.852174034285714

00:12:36.644 --> 00:12:39.955 target the glycine site as a way of more

NOTE Confidence: 0.852174034285714

00:12:39.955 --> 00:12:43.179 fine tune in the NMDA receptor complex.
NOTE Confidence: 0.852174034285714

00:12:43.180 --> 00:12:45.574 None of them have panned out as of yet,
NOTE Confidence: 0.852174034285714

00:12:45.580 --> 00:12:47.953 and then one can pursue at the
NOTE Confidence: 0.852174034285714

00:12:47.953 --> 00:12:49.700 subunit in order to be so.
NOTE Confidence: 0.852174034285714

00:12:49.700 --> 00:12:51.800 These are just high level examples
NOTE Confidence: 0.852174034285714

00:12:51.800 --> 00:12:54.280 of some of the drugs in play.
NOTE Confidence: 0.852174034285714

00:12:54.280 --> 00:12:56.520 Now to summary the brief summary to this
NOTE Confidence: 0.852174034285714

00:12:56.520 --> 00:12:58.971 point is TRD is to field and at the
NOTE Confidence: 0.852174034285714

00:12:58.971 --> 00:13:01.080 present trials it's a clinical definition,
NOTE Confidence: 0.852174034285714

00:13:01.080 --> 00:13:04.800 but we have to move away to that in consider
NOTE Confidence: 0.852174034285714

00:13:04.890 --> 00:13:08.308 biological means of defining TRD and MDA.
NOTE Confidence: 0.852174034285714

00:13:08.308 --> 00:13:10.432 Receptor inhibition may not be the
NOTE Confidence: 0.852174034285714

00:13:10.432 --> 00:13:11.899 primary mechanism of ketamine.
NOTE Confidence: 0.852174034285714

00:13:11.900 --> 00:13:15.005 I know that's not all schools agree on that,
NOTE Confidence: 0.852174034285714

00:13:15.010 --> 00:13:17.075 but we have some evidence of that.
NOTE Confidence: 0.852174034285714

00:13:17.080 --> 00:13:19.730 Psychedelic drugs are being explored

NOTE Confidence: 0.852174034285714
00:13:19.730 --> 00:13:20.840 in large studies.
NOTE Confidence: 0.852174034285714
00:13:20.840 --> 00:13:22.690 We'll know soon in the
NOTE Confidence: 0.852174034285714
00:13:22.690 --> 00:13:23.780 glutamatergic modulates with.
NOTE Confidence: 0.852174034285714
00:13:23.780 --> 00:13:25.680 Diverging modulates as well seems
NOTE Confidence: 0.852174034285714
00:13:25.680 --> 00:13:28.250 to be a promising group of drugs.
NOTE Confidence: 0.852174034285714
00:13:28.250 --> 00:13:31.430 Now in terms of mechanism action,
NOTE Confidence: 0.852174034285714
00:13:31.430 --> 00:13:34.215 this study raised whether opioid
NOTE Confidence: 0.852174034285714
00:13:34.215 --> 00:13:36.443 receptors might be implicated.
NOTE Confidence: 0.852174034285714
00:13:36.450 --> 00:13:38.175 This is studied by Williams
NOTE Confidence: 0.852174034285714
00:13:38.175 --> 00:13:39.822 and Alan Schatzberg's group,
NOTE Confidence: 0.852174034285714
00:13:39.822 --> 00:13:43.137 which you see here is that the
NOTE Confidence: 0.852174034285714
00:13:43.137 --> 00:13:44.965 the ketamine subjects treated
NOTE Confidence: 0.852174034285714
00:13:44.965 --> 00:13:47.250 with ketamine were pretreated with
NOTE Confidence: 0.852174034285714
00:13:47.319 --> 00:13:49.467 either placebo or say a placebo,
NOTE Confidence: 0.852174034285714
00:13:49.470 --> 00:13:50.943 saline or naltrexone.
NOTE Confidence: 0.852174034285714

00:13:50.943 --> 00:13:52.416 What you see,
NOTE Confidence: 0.852174034285714

00:13:52.420 --> 00:13:54.400 which is a new opioid antagonist.
NOTE Confidence: 0.852174034285714

00:13:54.400 --> 00:13:56.339 What you see is a diminishing or
NOTE Confidence: 0.852174034285714

00:13:56.339 --> 00:13:58.479 attenuation of the antidepressant effects,
NOTE Confidence: 0.852174034285714

00:13:58.480 --> 00:14:00.780 but the dissociate side effects
NOTE Confidence: 0.852174034285714

00:14:00.780 --> 00:14:03.659 do not diminish with the use of
NOTE Confidence: 0.852174034285714

00:14:03.660 --> 00:14:07.290 naltrexone work by Matt Klein.
NOTE Confidence: 0.911613938

00:14:09.490 --> 00:14:12.918 They argue that it's not an effect as
NOTE Confidence: 0.911613938

00:14:12.918 --> 00:14:15.790 an opiate, but more that it affects
NOTE Confidence: 0.911613938

00:14:15.790 --> 00:14:17.970 both NMDA and opioid signaling,
NOTE Confidence: 0.911613938

00:14:17.970 --> 00:14:19.690 and so that's something to
NOTE Confidence: 0.911613938

00:14:19.690 --> 00:14:21.066 consider in future development.
NOTE Confidence: 0.911613938

00:14:21.070 --> 00:14:23.722 So we were quite intrigued with
NOTE Confidence: 0.911613938

00:14:23.722 --> 00:14:26.377 with these findings and decide to
NOTE Confidence: 0.911613938

00:14:26.377 --> 00:14:29.160 pursue this a little bit more. First,
NOTE Confidence: 0.911613938

00:14:29.160 --> 00:14:31.750 a very brief summary of racemic Academy.

NOTE Confidence: 0.911613938

00:14:31.750 --> 00:14:32.794 When administered,

NOTE Confidence: 0.911613938

00:14:32.794 --> 00:14:36.282 you have within a few minutes in

NOTE Confidence: 0.911613938

00:14:36.282 --> 00:14:38.812 mice or in humans, 24 metabolites.

NOTE Confidence: 0.911613938

00:14:38.812 --> 00:14:41.617 Over 24 potentially different drugs.

NOTE Confidence: 0.911613938

00:14:41.620 --> 00:14:44.273 Towards the right you see here the

NOTE Confidence: 0.911613938

00:14:44.273 --> 00:14:47.187 pathway of our ketamine can be metabolized

NOTE Confidence: 0.911613938

00:14:47.187 --> 00:14:51.722 to to R6RH K or esketamine to 26S
H&K.

NOTE Confidence: 0.911613938

00:14:51.722 --> 00:14:53.327 They do not enter convert

NOTE Confidence: 0.911613938

00:14:53.327 --> 00:14:55.319 and so these two compounds,

NOTE Confidence: 0.911613938

00:14:55.320 --> 00:14:57.664 the two or six are in the two

NOTE Confidence: 0.911613938

00:14:57.664 --> 00:14:59.440 success do have antidepressant

NOTE Confidence: 0.911613938

00:14:59.440 --> 00:15:02.215 like properties in animal models.

NOTE Confidence: 0.911613938

00:15:02.220 --> 00:15:04.390 So this work was done and collaboration

NOTE Confidence: 0.911613938

00:15:04.390 --> 00:15:06.847 is was done in a Mike Michaelides

NOTE Confidence: 0.911613938

00:15:06.847 --> 00:15:08.307 lab by Jordy Buenaventura,

NOTE Confidence: 0.911613938

00:15:08.310 --> 00:15:10.902 and we were interested in better

NOTE Confidence: 0.911613938

00:15:10.902 --> 00:15:12.630 characterizing the the pharmacology

NOTE Confidence: 0.911613938

00:15:12.698 --> 00:15:14.670 of Esketamine versus archenemy.

NOTE Confidence: 0.911613938

00:15:14.670 --> 00:15:17.574 Here we see a screening receptor

NOTE Confidence: 0.911613938

00:15:17.574 --> 00:15:19.510 enzyme profile in here.

NOTE Confidence: 0.911613938

00:15:19.510 --> 00:15:20.566 It's very tiny,

NOTE Confidence: 0.911613938

00:15:20.566 --> 00:15:22.678 all the different receptors and enzymes,

NOTE Confidence: 0.911613938

00:15:22.680 --> 00:15:24.986 and what you find is, not surprisingly,

NOTE Confidence: 0.911613938

00:15:24.986 --> 00:15:28.724 both S cademy and our ketamine.

NOTE Confidence: 0.911613938

00:15:28.730 --> 00:15:29.716 Bind PCP,

NOTE Confidence: 0.911613938

00:15:29.716 --> 00:15:33.167 But what was interesting here is we

NOTE Confidence: 0.911613938

00:15:33.167 --> 00:15:36.661 found that as ketamine at 10 micro

NOTE Confidence: 0.911613938

00:15:36.661 --> 00:15:40.970 molar was binding to muoio receptors.

NOTE Confidence: 0.911613938

00:15:40.970 --> 00:15:43.310 When you look at competitive radioligand

NOTE Confidence: 0.911613938

00:15:43.310 --> 00:15:45.220 binding essays towards the left,

NOTE Confidence: 0.911613938

00:15:45.220 --> 00:15:47.148 you have MK to one for an MDA.
NOTE Confidence: 0.911613938

00:15:47.150 --> 00:15:48.990 Receptors in orange is.
NOTE Confidence: 0.911613938

00:15:48.990 --> 00:15:49.910 That's ketamine.
NOTE Confidence: 0.911613938

00:15:49.910 --> 00:15:51.746 You see that the displacement is
NOTE Confidence: 0.911613938

00:15:51.746 --> 00:15:53.810 greater for S compared to R ketamine.
NOTE Confidence: 0.911613938

00:15:53.810 --> 00:15:56.114 We know that that S is already four
NOTE Confidence: 0.911613938

00:15:56.114 --> 00:15:58.552 times more potent than archenemy, but.
NOTE Confidence: 0.911613938

00:15:58.552 --> 00:16:00.448 Where are opioid receptors?
NOTE Confidence: 0.911613938

00:16:00.450 --> 00:16:02.410 They're they're summarized down here.
NOTE Confidence: 0.911613938

00:16:02.410 --> 00:16:04.909 New opioid receptor is greater for S,
NOTE Confidence: 0.911613938

00:16:04.910 --> 00:16:07.185 the S and antiwar compared to R,
NOTE Confidence: 0.911613938

00:16:07.190 --> 00:16:09.507 and also for the capital opioid receptor.
NOTE Confidence: 0.911613938

00:16:09.510 --> 00:16:10.626 For the Sigma,
NOTE Confidence: 0.911613938

00:16:10.626 --> 00:16:13.214 it's the flip side R in anterior,
NOTE Confidence: 0.911613938

00:16:13.214 --> 00:16:15.386 as greater effects on Sigma receptors
NOTE Confidence: 0.911613938

00:16:15.386 --> 00:16:17.872 and Sigma have been implicated in

NOTE Confidence: 0.911613938

00:16:17.872 --> 00:16:19.987 antidepressant like properties as well.

NOTE Confidence: 0.911613938

00:16:19.990 --> 00:16:22.926 The study went on to look at FDG

NOTE Confidence: 0.911613938

00:16:22.926 --> 00:16:25.169 PET imaging in awake rodents,

NOTE Confidence: 0.911613938

00:16:25.170 --> 00:16:27.578 looking at the US versus the ordinance

NOTE Confidence: 0.911613938

00:16:27.578 --> 00:16:30.147 timers and what you see with the S

NOTE Confidence: 0.911613938

00:16:30.147 --> 00:16:32.168 is that there's increase in activity

NOTE Confidence: 0.911613938

00:16:32.168 --> 00:16:34.108 and medial prefrontal cortex.

NOTE Confidence: 0.911613938

00:16:34.110 --> 00:16:36.058 Where the opioid receptors

NOTE Confidence: 0.911613938

00:16:36.058 --> 00:16:38.006 reside largely in part,

NOTE Confidence: 0.911613938

00:16:38.010 --> 00:16:40.298 and then you have the Aryan nation where

NOTE Confidence: 0.911613938

00:16:40.298 --> 00:16:43.348 what you find is a decrease activity and

NOTE Confidence: 0.911613938

00:16:43.348 --> 00:16:44.960 paraventricular in habenular regions.

NOTE Confidence: 0.911613938

00:16:44.960 --> 00:16:48.467 Keep in mind some studies suggest that

NOTE Confidence: 0.911613938

00:16:48.467 --> 00:16:50.942 there's hyperactivity of the habenula

NOTE Confidence: 0.911613938

00:16:50.942 --> 00:16:54.036 and involved in the NT reward system.

NOTE Confidence: 0.911613938

00:16:54.040 --> 00:16:56.085 When you look at autoradiography
NOTE Confidence: 0.911613938

00:16:56.085 --> 00:16:58.956 studies you see on the top is
NOTE Confidence: 0.911613938

00:16:58.956 --> 00:17:01.150 middle is esketamine you see the
NOTE Confidence: 0.911613938

00:17:01.150 --> 00:17:02.800 effects of mule period receptors.
NOTE Confidence: 0.911613938

00:17:02.800 --> 00:17:03.814 It's reversed with.
NOTE Confidence: 0.911613938

00:17:03.814 --> 00:17:05.741 Now trick with that, sorry,
NOTE Confidence: 0.911613938

00:17:05.741 --> 00:17:06.883 not naloxone,
NOTE Confidence: 0.911613938

00:17:06.883 --> 00:17:09.167 whereas there's no significant
NOTE Confidence: 0.911613938

00:17:09.167 --> 00:17:11.465 changes with our ketamine here.
NOTE Confidence: 0.911613938

00:17:11.465 --> 00:17:14.160 You can see the right basil increase
NOTE Confidence: 0.911613938

00:17:14.230 --> 00:17:16.398 with morphine increases with
NOTE Confidence: 0.911613938

00:17:16.398 --> 00:17:18.566 Esketamine reverse with naloxone.
NOTE Confidence: 0.911613938

00:17:18.570 --> 00:17:20.878 No significant changes with
NOTE Confidence: 0.911613938

00:17:20.878 --> 00:17:23.186 our the our enantiomer.
NOTE Confidence: 0.911613938

00:17:23.190 --> 00:17:27.447 The study next went on to look at the
NOTE Confidence: 0.911613938

00:17:27.447 --> 00:17:31.062 behavioral effects of these enantiomers

NOTE Confidence: 0.911613938

00:17:31.062 --> 00:17:34.198 using classical behavioral procedures.

NOTE Confidence: 0.911613938

00:17:34.200 --> 00:17:35.700 That characterize opioid

NOTE Confidence: 0.911613938

00:17:35.700 --> 00:17:37.200 in psychostimulant drugs.

NOTE Confidence: 0.911613938

00:17:37.200 --> 00:17:38.355 And here you're going to

NOTE Confidence: 0.911613938

00:17:38.355 --> 00:17:39.510 see an orange is the

NOTE Confidence: 0.825059270476191

00:17:39.566 --> 00:17:41.444 esketamine is the one that's elevated

NOTE Confidence: 0.825059270476191

00:17:41.444 --> 00:17:43.320 in all these behavioral procedures.

NOTE Confidence: 0.825059270476191

00:17:43.320 --> 00:17:44.554 Acute locomotion,

NOTE Confidence: 0.825059270476191

00:17:44.554 --> 00:17:47.639 locomotor sensitization compared to R,

NOTE Confidence: 0.825059270476191

00:17:47.640 --> 00:17:49.590 cross sensitization, and when you look

NOTE Confidence: 0.825059270476191

00:17:49.590 --> 00:17:51.540 at the condition place preference,

NOTE Confidence: 0.825059270476191

00:17:51.540 --> 00:17:52.950 you see it's greater with

NOTE Confidence: 0.825059270476191

00:17:52.950 --> 00:17:54.360 the S and then timer.

NOTE Confidence: 0.825059270476191

00:17:54.360 --> 00:17:56.900 No significant changes with R.

NOTE Confidence: 0.825059270476191

00:17:56.900 --> 00:17:59.396 What about drug sale fund ministratation?

NOTE Confidence: 0.825059270476191

00:17:59.400 --> 00:18:01.236 You also seen the dose response.
NOTE Confidence: 0.825059270476191

00:18:01.240 --> 00:18:04.705 Greater increases with as compared to R.
NOTE Confidence: 0.825059270476191

00:18:04.710 --> 00:18:06.910 But in the extinction phase,
NOTE Confidence: 0.825059270476191

00:18:06.910 --> 00:18:09.568 what was distinct from opium psychostimulant
NOTE Confidence: 0.825059270476191

00:18:09.568 --> 00:18:12.702 drugs is that there was extinction and
NOTE Confidence: 0.825059270476191

00:18:12.702 --> 00:18:15.282 suggests that it's not habit forming,
NOTE Confidence: 0.825059270476191

00:18:15.290 --> 00:18:16.706 so they are quite.
NOTE Confidence: 0.825059270476191

00:18:16.706 --> 00:18:18.476 These enantiomers are quite distinct
NOTE Confidence: 0.825059270476191

00:18:18.476 --> 00:18:20.917 in the opioids and psychostimulants.
NOTE Confidence: 0.825059270476191

00:18:20.920 --> 00:18:21.904 To summarize,
NOTE Confidence: 0.825059270476191

00:18:21.904 --> 00:18:24.856 intervene at this to this point.
NOTE Confidence: 0.825059270476191

00:18:24.860 --> 00:18:29.018 Self administration was for the Esplanade ER.
NOTE Confidence: 0.825059270476191

00:18:29.020 --> 00:18:32.206 We see that the classical behavioral
NOTE Confidence: 0.825059270476191

00:18:32.206 --> 00:18:34.370 procedures separated the S from the
NOTE Confidence: 0.825059270476191

00:18:34.370 --> 00:18:37.483 R and in summary we see that there
NOTE Confidence: 0.825059270476191

00:18:37.483 --> 00:18:40.285 is a divergent in the behavioral

NOTE Confidence: 0.825059270476191
00:18:40.285 --> 00:18:42.122 pharmacological effects of these
NOTE Confidence: 0.825059270476191
00:18:42.122 --> 00:18:43.938 different enantiomers and it
NOTE Confidence: 0.825059270476191
00:18:43.938 --> 00:18:46.078 suggests that the abuse liability
NOTE Confidence: 0.825059270476191
00:18:46.078 --> 00:18:49.120 is more on the US side versus the R.
NOTE Confidence: 0.825059270476191
00:18:49.120 --> 00:18:50.536 Keep in mind what we're saying.
NOTE Confidence: 0.825059270476191
00:18:50.540 --> 00:18:51.404 What I'm saying here.
NOTE Confidence: 0.825059270476191
00:18:51.404 --> 00:18:51.620 Also,
NOTE Confidence: 0.825059270476191
00:18:51.620 --> 00:18:55.616 is that the racemic the S and the are
NOTE Confidence: 0.825059270476191
00:18:55.616 --> 00:18:58.607 enantiomers do share common properties,
NOTE Confidence: 0.825059270476191
00:18:58.610 --> 00:19:01.316 but they also may be different
NOTE Confidence: 0.825059270476191
00:19:01.320 --> 00:19:04.230 types of drugs and may have
NOTE Confidence: 0.825059270476191
00:19:04.230 --> 00:19:05.685 different therapeutic applications.
NOTE Confidence: 0.825059270476191
00:19:05.690 --> 00:19:09.323 So we wanna study wanted to identify
NOTE Confidence: 0.825059270476191
00:19:09.323 --> 00:19:13.330 more the the mechanism of ketamine.
NOTE Confidence: 0.825059270476191
00:19:13.330 --> 00:19:16.718 And we designed this study a few years back.
NOTE Confidence: 0.825059270476191

00:19:16.718 --> 00:19:18.502 It's called the ketamine's mechanism
NOTE Confidence: 0.825059270476191

00:19:18.502 --> 00:19:21.554 of action study the kit MOA where
NOTE Confidence: 0.825059270476191

00:19:21.554 --> 00:19:24.004 we where we obtain information
NOTE Confidence: 0.825059270476191

00:19:24.004 --> 00:19:26.424 at various levels of biology.
NOTE Confidence: 0.825059270476191

00:19:26.430 --> 00:19:28.334 I'm using multiscale systems
NOTE Confidence: 0.825059270476191

00:19:28.334 --> 00:19:30.238 biology approach and integrating
NOTE Confidence: 0.825059270476191

00:19:30.238 --> 00:19:32.669 a wide range of behavioral,
NOTE Confidence: 0.825059270476191

00:19:32.670 --> 00:19:35.736 clinical and other technologies shown here.
NOTE Confidence: 0.825059270476191

00:19:35.740 --> 00:19:38.284 And these where we where we
NOTE Confidence: 0.825059270476191

00:19:38.284 --> 00:19:41.750 where we obtain repeat measures.
NOTE Confidence: 0.825059270476191

00:19:41.750 --> 00:19:45.033 Now I want to summarize briefly as
NOTE Confidence: 0.825059270476191

00:19:45.033 --> 00:19:47.854 introducing the kid MOA study is I
NOTE Confidence: 0.825059270476191

00:19:47.854 --> 00:19:49.871 already mentioned that ketamine binds
NOTE Confidence: 0.825059270476191

00:19:49.871 --> 00:19:52.670 to the NMD? The NMDA receptor Gabbert.
NOTE Confidence: 0.825059270476191

00:19:52.670 --> 00:19:56.034 You can turn neurons and there's this in.
NOTE Confidence: 0.825059270476191

00:19:56.034 --> 00:19:57.968 Inhibition. Excitation occurs.

NOTE Confidence: 0.825059270476191

00:19:57.968 --> 00:20:01.738 Glutamate release occurs with ketamine.

NOTE Confidence: 0.825059270476191

00:20:01.740 --> 00:20:04.232 The other drug Canada drug we are

NOTE Confidence: 0.825059270476191

00:20:04.232 --> 00:20:06.978 looking at is Manglore 2 antagonist

NOTE Confidence: 0.825059270476191

00:20:06.980 --> 00:20:10.958 and we are also looking at the son of

NOTE Confidence: 0.825059270476191

00:20:10.958 --> 00:20:13.940 it ketamine to our six origin key.

NOTE Confidence: 0.825059270476191

00:20:13.940 --> 00:20:16.598 Also as a property of enhancing

NOTE Confidence: 0.825059270476191

00:20:16.598 --> 00:20:18.780 glutamate release without blocking NMDA.

NOTE Confidence: 0.825059270476191

00:20:18.780 --> 00:20:19.158 Thus,

NOTE Confidence: 0.825059270476191

00:20:19.158 --> 00:20:21.426 in theory you would not have

NOTE Confidence: 0.825059270476191

00:20:21.426 --> 00:20:22.560 the psychotomimetic effects.

NOTE Confidence: 0.825059270476191

00:20:22.560 --> 00:20:27.082 This study was done in Hussain Imanx's

NOTE Confidence: 0.825059270476191

00:20:27.082 --> 00:20:29.560 lab and what was found here is,

NOTE Confidence: 0.825059270476191

00:20:29.560 --> 00:20:30.250 of course,

NOTE Confidence: 0.825059270476191

00:20:30.250 --> 00:20:32.320 ketamine decreases the force swim test,

NOTE Confidence: 0.825059270476191

00:20:32.320 --> 00:20:33.096 the immobilien,

NOTE Confidence: 0.825059270476191

00:20:33.096 --> 00:20:35.036 the force swim test significant
NOTE Confidence: 0.825059270476191

00:20:35.036 --> 00:20:36.680 signifying and depression effects,
NOTE Confidence: 0.825059270476191

00:20:36.680 --> 00:20:39.056 but based on follow up work
NOTE Confidence: 0.825059270476191

00:20:39.056 --> 00:20:41.160 by beta Maugham at Yale.
NOTE Confidence: 0.825059270476191

00:20:41.160 --> 00:20:44.277 What was done here is we used NBQ
NOTE Confidence: 0.825059270476191

00:20:44.277 --> 00:20:46.790 mix and an AMP antagonist and the
NOTE Confidence: 0.825059270476191

00:20:46.871 --> 00:20:49.183 behavioral effects of ketamine
NOTE Confidence: 0.825059270476191

00:20:49.183 --> 00:20:51.495 were attenuated or blocked.
NOTE Confidence: 0.825059270476191

00:20:51.500 --> 00:20:52.672 So just in that.
NOTE Confidence: 0.825059270476191

00:20:52.672 --> 00:20:54.430 AMPA throughput is important to the
NOTE Confidence: 0.825059270476191

00:20:54.493 --> 00:20:56.469 antidepressant effects of ketamine,
NOTE Confidence: 0.825059270476191

00:20:56.470 --> 00:20:58.110 and so these different drugs
NOTE Confidence: 0.825059270476191

00:20:58.110 --> 00:21:00.105 they mentioned as Canada drugs do
NOTE Confidence: 0.825059270476191

00:21:00.105 --> 00:21:01.585 have that property in common.
NOTE Confidence: 0.825059270476191

00:21:01.590 --> 00:21:02.640 In addition,
NOTE Confidence: 0.825059270476191

00:21:02.640 --> 00:21:05.265 they also in preclinical studies,

NOTE Confidence: 0.825059270476191

00:21:05.270 --> 00:21:06.770 increase gamma power,

NOTE Confidence: 0.825059270476191

00:21:06.770 --> 00:21:08.270 which represents this

NOTE Confidence: 0.825059270476191

00:21:08.270 --> 00:21:09.270 neuronal synchronization.

NOTE Confidence: 0.825059270476191

00:21:09.270 --> 00:21:11.629 So could this be a cross species

NOTE Confidence: 0.825059270476191

00:21:11.629 --> 00:21:13.767 biomarker that we could use to

NOTE Confidence: 0.825059270476191

00:21:13.767 --> 00:21:16.820 develop drugs in here we are using

NOTE Confidence: 0.825059270476191

00:21:16.820 --> 00:21:19.170 several tools to examine plasticity,

NOTE Confidence: 0.8080954

00:21:19.170 --> 00:21:21.876 potentiation humans and they are gamma,

NOTE Confidence: 0.8080954

00:21:21.880 --> 00:21:25.030 power, slow, wave. Activity and TMS.

NOTE Confidence: 0.8080954

00:21:25.030 --> 00:21:25.870 In the interest of time,

NOTE Confidence: 0.8080954

00:21:25.870 --> 00:21:27.826 I might have only ability to

NOTE Confidence: 0.8080954

00:21:27.826 --> 00:21:30.128 talk about one or two of these,

NOTE Confidence: 0.8080954

00:21:30.130 --> 00:21:31.978 but this is a new study that's

NOTE Confidence: 0.8080954

00:21:31.978 --> 00:21:33.446 still underway, should be completed,

NOTE Confidence: 0.8080954

00:21:33.446 --> 00:21:35.006 hopefully in the near future,

NOTE Confidence: 0.8080954

00:21:35.010 --> 00:21:36.534 and it's called the new barrack
NOTE Confidence: 0.8080954

00:21:36.534 --> 00:21:37.550 study and I'll summarize,
NOTE Confidence: 0.8080954

00:21:37.550 --> 00:21:39.850 which is basically examining
NOTE Confidence: 0.8080954

00:21:39.850 --> 00:21:42.150 the effects of ketamine.
NOTE Confidence: 0.8080954

00:21:42.150 --> 00:21:43.410 In the scanner,
NOTE Confidence: 0.8080954

00:21:43.410 --> 00:21:46.871 subjects receiving fMRI and EEG and the same
NOTE Confidence: 0.8080954

00:21:46.871 --> 00:21:49.944 subject receiving a later time point EMG,
NOTE Confidence: 0.8080954

00:21:49.950 --> 00:21:52.464 and then repeat administration and higher
NOTE Confidence: 0.8080954

00:21:52.464 --> 00:21:55.770 low dose of ketamine with repeat biomarkers.
NOTE Confidence: 0.8080954

00:21:55.770 --> 00:21:58.045 This is the the earlier study that
NOTE Confidence: 0.8080954

00:21:58.045 --> 00:22:00.238 kit MOA study that I mentioned.
NOTE Confidence: 0.8080954

00:22:00.240 --> 00:22:02.670 Single infusion of ketamine or placebo,
NOTE Confidence: 0.8080954

00:22:02.670 --> 00:22:04.462 unmedicated depressed subjects and
NOTE Confidence: 0.8080954

00:22:04.462 --> 00:22:07.150 after two weeks crossover pretty much
NOTE Confidence: 0.8080954

00:22:07.220 --> 00:22:09.908 the design of previous ketamine studies
NOTE Confidence: 0.8080954

00:22:09.908 --> 00:22:12.330 but with longitudinal biomarkers subjects.

NOTE Confidence: 0.8080954

00:22:12.330 --> 00:22:15.294 Here now 35 have treatment resistant

NOTE Confidence: 0.8080954

00:22:15.294 --> 00:22:17.798 depression or medication free and

NOTE Confidence: 0.8080954

00:22:17.798 --> 00:22:20.043 then control subjects also received

NOTE Confidence: 0.8080954

00:22:20.043 --> 00:22:22.792 ketamine at the same time points

NOTE Confidence: 0.8080954

00:22:22.792 --> 00:22:24.540 in the same biomarkers.

NOTE Confidence: 0.8080954

00:22:24.540 --> 00:22:27.660 Subjects here were moderately depressed.

NOTE Confidence: 0.8080954

00:22:27.660 --> 00:22:30.030 They 40% had previous suicide attempts

NOTE Confidence: 0.8080954

00:22:30.030 --> 00:22:33.439 and it's a very rich data set that that

NOTE Confidence: 0.8080954

00:22:33.439 --> 00:22:36.658 I'm going to summarize a few of the studies,

NOTE Confidence: 0.8080954

00:22:36.660 --> 00:22:37.522 for example,

NOTE Confidence: 0.8080954

00:22:37.522 --> 00:22:41.420 one each subject may have had five F MRI,

NOTE Confidence: 0.8080954

00:22:41.420 --> 00:22:42.804 7 T,

NOTE Confidence: 0.8080954

00:22:42.804 --> 00:22:44.880 3T and polysomnography.

NOTE Confidence: 0.8080954

00:22:44.880 --> 00:22:46.980 And these are some of the publications

NOTE Confidence: 0.8080954

00:22:46.980 --> 00:22:48.748 have come out of that study.

NOTE Confidence: 0.8080954

00:22:48.750 --> 00:22:50.525 Just to show you consistent
NOTE Confidence: 0.8080954

00:22:50.525 --> 00:22:51.590 with prior studies,
NOTE Confidence: 0.8080954

00:22:51.590 --> 00:22:55.112 rapid onset within minutes lasting 11
NOTE Confidence: 0.8080954

00:22:55.112 --> 00:22:59.230 days here increases in CADS as expected.
NOTE Confidence: 0.8080954

00:22:59.230 --> 00:23:01.925 But what you see is different than
NOTE Confidence: 0.8080954

00:23:01.925 --> 00:23:04.069 standard convention and at present
NOTE Confidence: 0.8080954

00:23:04.069 --> 00:23:05.901 it's broad therapeutic effects
NOTE Confidence: 0.8080954

00:23:05.901 --> 00:23:08.540 improvements in the anxiety and edonia,
NOTE Confidence: 0.8080954

00:23:08.540 --> 00:23:11.530 anticipatory consummatory and PTSD symptoms,
NOTE Confidence: 0.8080954

00:23:11.530 --> 00:23:13.650 as well as functioning.
NOTE Confidence: 0.8080954

00:23:13.650 --> 00:23:14.180 Unexpectedly,
NOTE Confidence: 0.8080954

00:23:14.180 --> 00:23:17.344 what we found was the that healthy
NOTE Confidence: 0.8080954

00:23:17.344 --> 00:23:20.182 volunteers developed a increase in
NOTE Confidence: 0.8080954

00:23:20.182 --> 00:23:22.276 depressive symptoms temporarily,
NOTE Confidence: 0.8080954

00:23:22.280 --> 00:23:24.744 which did not correlate with the changes
NOTE Confidence: 0.8080954

00:23:24.744 --> 00:23:27.419 of of the dissociative symptoms.

NOTE Confidence: 0.8080954
00:23:27.420 --> 00:23:29.012 Subjects reported in their
NOTE Confidence: 0.8080954
00:23:29.012 --> 00:23:31.400 attention lasted to an ability to
NOTE Confidence: 0.8080954
00:23:31.468 --> 00:23:33.058 feel emotional blunting,
NOTE Confidence: 0.8080954
00:23:33.060 --> 00:23:35.960 which was not a prolonged.
NOTE Confidence: 0.8080954
00:23:35.960 --> 00:23:37.262 To summarize here,
NOTE Confidence: 0.8080954
00:23:37.262 --> 00:23:38.998 information at the circuit
NOTE Confidence: 0.8080954
00:23:38.998 --> 00:23:40.863 level here subjects received
NOTE Confidence: 0.8080954
00:23:40.863 --> 00:23:42.839 a single infusion crossover,
NOTE Confidence: 0.8080954
00:23:42.840 --> 00:23:45.235 unmedicated baseline 3T MRI in
NOTE Confidence: 0.8080954
00:23:45.235 --> 00:23:49.215 a two and a 10 days to capture
NOTE Confidence: 0.8080954
00:23:49.215 --> 00:23:52.224 the on off effects of ketamine.
NOTE Confidence: 0.8080954
00:23:52.224 --> 00:23:52.768 Specifically,
NOTE Confidence: 0.8080954
00:23:52.768 --> 00:23:56.576 looking at the default mode network settings,
NOTE Confidence: 0.8080954
00:23:56.580 --> 00:23:59.340 network and central executive network.
NOTE Confidence: 0.8080954
00:23:59.340 --> 00:24:01.200 Consistent with has been reported,
NOTE Confidence: 0.8080954

00:24:01.200 --> 00:24:02.980 we find decreases in depressive
NOTE Confidence: 0.8080954

00:24:02.980 --> 00:24:05.381 symptoms by two days and the effects
NOTE Confidence: 0.8080954

00:24:05.381 --> 00:24:08.020 start to wear off by 10 days in green.
NOTE Confidence: 0.8080954

00:24:08.020 --> 00:24:10.930 No significant changes in the the
NOTE Confidence: 0.8080954

00:24:10.930 --> 00:24:13.548 sailing condition when you link this
NOTE Confidence: 0.8080954

00:24:13.548 --> 00:24:15.744 with neuroimaging at precisely the
NOTE Confidence: 0.8080954

00:24:15.744 --> 00:24:18.922 same time points which you find here
NOTE Confidence: 0.8080954

00:24:18.922 --> 00:24:21.005 at baseline is increased difference
NOTE Confidence: 0.8080954

00:24:21.005 --> 00:24:22.930 between patients and healthy controls,
NOTE Confidence: 0.8080954

00:24:22.930 --> 00:24:24.880 and insula the salience network.
NOTE Confidence: 0.8080954

00:24:24.880 --> 00:24:27.197 Not functioning well at the peak of
NOTE Confidence: 0.8080954

00:24:27.197 --> 00:24:29.300 improvement of the present symptoms.
NOTE Confidence: 0.8080954

00:24:29.300 --> 00:24:31.340 No longer significant increases in
NOTE Confidence: 0.8080954

00:24:31.340 --> 00:24:33.380 hyperactivity of the insula and
NOTE Confidence: 0.8080954

00:24:33.450 --> 00:24:35.571 then by day 10 when the effects
NOTE Confidence: 0.8080954

00:24:35.571 --> 00:24:37.288 of ketamine start to wear off.

NOTE Confidence: 0.8080954

00:24:37.290 --> 00:24:40.746 You see a return of the activation of

NOTE Confidence: 0.8080954

00:24:40.746 --> 00:24:44.156 insulin, so this nice on off effect.

NOTE Confidence: 0.8080954

00:24:44.160 --> 00:24:44.651 Subsequently,

NOTE Confidence: 0.8080954

00:24:44.651 --> 00:24:48.088 and a hit was interested in antidote

NOTE Confidence: 0.8080954

00:24:48.088 --> 00:24:49.627 and corticostriatal circuitry

NOTE Confidence: 0.8080954

00:24:49.627 --> 00:24:52.531 into the question was that there's

NOTE Confidence: 0.8080954

00:24:52.531 --> 00:24:53.983 ketamine affect cortical

NOTE Confidence: 0.731726679954545

00:24:54.056 --> 00:24:55.390 striatal circuitry,

NOTE Confidence: 0.731726679954545

00:24:55.390 --> 00:24:56.940 and the answer is yes.

NOTE Confidence: 0.731726679954545

00:24:56.940 --> 00:25:01.520 Here 33 unmedicated patients,

NOTE Confidence: 0.731726679954545

00:25:01.520 --> 00:25:03.314 25 healthy controls,

NOTE Confidence: 0.731726679954545

00:25:03.314 --> 00:25:06.304 arresting state of eight minutes.

NOTE Confidence: 0.731726679954545

00:25:06.310 --> 00:25:07.870 And these are the seed regions,

NOTE Confidence: 0.731726679954545

00:25:07.870 --> 00:25:10.870 dorsal kodia, ventral stratium, ventral,

NOTE Confidence: 0.731726679954545

00:25:10.870 --> 00:25:16.018 rostral putamen and dorsal caudal putamen.

NOTE Confidence: 0.731726679954545

00:25:16.020 --> 00:25:20.136 And what you see here are the
NOTE Confidence: 0.731726679954545

00:25:20.136 --> 00:25:21.880 global differences in racemic,
NOTE Confidence: 0.731726679954545

00:25:21.880 --> 00:25:24.645 ketamine, and whole brain functional
NOTE Confidence: 0.731726679954545

00:25:24.645 --> 00:25:27.395 connectivity across the forest seeds.
NOTE Confidence: 0.731726679954545

00:25:27.395 --> 00:25:30.070 Ventral freedom with dorsal lateral
NOTE Confidence: 0.731726679954545

00:25:30.070 --> 00:25:31.596 dorsal cardia, ventrolateral,
NOTE Confidence: 0.731726679954545

00:25:31.596 --> 00:25:33.876 conflict zone, and so forth.
NOTE Confidence: 0.731726679954545

00:25:33.880 --> 00:25:36.880 But to summarize here you see in green,
NOTE Confidence: 0.731726679954545

00:25:36.880 --> 00:25:38.955 placebo, orange, ketamine you see
NOTE Confidence: 0.731726679954545

00:25:38.955 --> 00:25:40.615 throughout the different seeds.
NOTE Confidence: 0.731726679954545

00:25:40.620 --> 00:25:42.990 If you're a healthy, controlled subject,
NOTE Confidence: 0.731726679954545

00:25:42.990 --> 00:25:45.858 you have decreased in the hole.
NOTE Confidence: 0.731726679954545

00:25:45.860 --> 00:25:47.303 Brain functional connectivity.
NOTE Confidence: 0.731726679954545

00:25:47.303 --> 00:25:50.189 If you have treatment resistant depression,
NOTE Confidence: 0.731726679954545

00:25:50.190 --> 00:25:53.228 you have an increase in this connectivity.
NOTE Confidence: 0.731726679954545

00:25:53.230 --> 00:25:56.326 So opposite directions in at the

NOTE Confidence: 0.731726679954545

00:25:56.326 --> 00:25:59.480 same time points towards the bottom.

NOTE Confidence: 0.731726679954545

00:25:59.480 --> 00:26:02.492 You see the correlation of the

NOTE Confidence: 0.731726679954545

00:26:02.492 --> 00:26:04.500 seed with the connectivity

NOTE Confidence: 0.731726679954545

00:26:04.596 --> 00:26:07.328 changes with depression scores.

NOTE Confidence: 0.731726679954545

00:26:07.330 --> 00:26:10.528 There's a very nice correlation of

NOTE Confidence: 0.731726679954545

00:26:10.528 --> 00:26:14.013 amongst the different seeds in a trend

NOTE Confidence: 0.731726679954545

00:26:14.013 --> 00:26:16.533 for the anhedonia with the chaps.

NOTE Confidence: 0.731726679954545

00:26:16.540 --> 00:26:19.420 Information at the six to to 8 hour,

NOTE Confidence: 0.731726679954545

00:26:19.420 --> 00:26:21.264 6 to 9 hours.

NOTE Confidence: 0.731726679954545

00:26:21.264 --> 00:26:22.186 After ketamine,

NOTE Confidence: 0.731726679954545

00:26:22.190 --> 00:26:25.654 we obtained a Meg and also at baseline

NOTE Confidence: 0.731726679954545

00:26:25.660 --> 00:26:29.036 and this is to get at this this

NOTE Confidence: 0.731726679954545

00:26:29.040 --> 00:26:32.300 interplay between excitation and ambition.

NOTE Confidence: 0.731726679954545

00:26:32.300 --> 00:26:34.316 What we use here is gamma power,

NOTE Confidence: 0.731726679954545

00:26:34.320 --> 00:26:36.805 neuronal stellations in the 30

NOTE Confidence: 0.731726679954545

00:26:36.805 --> 00:26:40.044 to 50 Hertz range so we can use
NOTE Confidence: 0.731726679954545

00:26:40.044 --> 00:26:41.599 this a cross species biomarker.
NOTE Confidence: 0.731726679954545

00:26:41.600 --> 00:26:45.480 So here this has been very well studied,
NOTE Confidence: 0.731726679954545

00:26:45.480 --> 00:26:46.276 you see.
NOTE Confidence: 0.731726679954545

00:26:46.276 --> 00:26:49.062 Up to 30 to 50 Hertz range,
NOTE Confidence: 0.731726679954545

00:26:49.070 --> 00:26:51.485 a change and early visual cortex and
NOTE Confidence: 0.731726679954545

00:26:51.485 --> 00:26:53.970 that has been previously reported,
NOTE Confidence: 0.731726679954545

00:26:53.970 --> 00:26:55.092 but Gamma also.
NOTE Confidence: 0.731726679954545

00:26:55.092 --> 00:26:56.962 Lations can be described in
NOTE Confidence: 0.731726679954545

00:26:56.962 --> 00:26:58.290 many different regions.
NOTE Confidence: 0.731726679954545

00:26:58.290 --> 00:26:59.156 Visual, sensory,
NOTE Confidence: 0.731726679954545

00:26:59.156 --> 00:27:00.022 motor cortex,
NOTE Confidence: 0.731726679954545

00:27:00.022 --> 00:27:03.128 auditory cortex and in some ways might
NOTE Confidence: 0.731726679954545

00:27:03.128 --> 00:27:05.293 represent plasticity phenomena and thus
NOTE Confidence: 0.731726679954545

00:27:05.293 --> 00:27:08.270 might be a useful putative biomarker
NOTE Confidence: 0.731726679954545

00:27:08.270 --> 00:27:10.610 to understand better understand.

NOTE Confidence: 0.731726679954545

00:27:10.610 --> 00:27:13.586 Ketamine gamma rhythms correlate

NOTE Confidence: 0.731726679954545

00:27:13.586 --> 00:27:16.400 with neuron action potentials.

NOTE Confidence: 0.731726679954545

00:27:16.400 --> 00:27:19.160 They are invading sensory

NOTE Confidence: 0.731726679954545

00:27:19.160 --> 00:27:21.580 perception information code in,

NOTE Confidence: 0.731726679954545

00:27:21.580 --> 00:27:23.440 especially in hippocampus,

NOTE Confidence: 0.731726679954545

00:27:23.440 --> 00:27:26.590 and during cognitive tasks Now what

NOTE Confidence: 0.731726679954545

00:27:26.590 --> 00:27:29.270 generates gamma part we don't know for sure,

NOTE Confidence: 0.731726679954545

00:27:29.270 --> 00:27:33.358 but some work suggests it's at the

NOTE Confidence: 0.731726679954545

00:27:33.358 --> 00:27:35.523 level of parvalbumin inhibitory's

NOTE Confidence: 0.731726679954545

00:27:35.523 --> 00:27:37.588 with the pyramidal cells excitation

NOTE Confidence: 0.731726679954545

00:27:37.588 --> 00:27:40.860 and what you see here are these micro

NOTE Confidence: 0.731726679954545

00:27:40.860 --> 00:27:42.800 circuits that have been described

NOTE Confidence: 0.731726679954545

00:27:42.800 --> 00:27:45.160 called the Interneuron network gamma,

NOTE Confidence: 0.731726679954545

00:27:45.160 --> 00:27:46.678 or the ping, when the pyramidal.

NOTE Confidence: 0.731726679954545

00:27:46.680 --> 00:27:47.406 Those involved.

NOTE Confidence: 0.731726679954545

00:27:47.406 --> 00:27:48.858 Why is this important?
NOTE Confidence: 0.731726679954545

00:27:48.860 --> 00:27:50.375 Well, with electrophysiological
NOTE Confidence: 0.731726679954545

00:27:50.375 --> 00:27:52.395 measures and five Tomic.
NOTE Confidence: 0.731726679954545

00:27:52.400 --> 00:27:53.766 Providing example,
NOTE Confidence: 0.731726679954545

00:27:53.766 --> 00:27:57.864 you can generate estimates of the
NOTE Confidence: 0.731726679954545

00:27:57.864 --> 00:28:01.098 excitation inhibition into formulas and
NOTE Confidence: 0.731726679954545

00:28:01.098 --> 00:28:03.846 then calculate the regional dynamics
NOTE Confidence: 0.731726679954545

00:28:03.846 --> 00:28:07.500 that are going on at this level.
NOTE Confidence: 0.731726679954545

00:28:07.500 --> 00:28:07.886 Now,
NOTE Confidence: 0.731726679954545

00:28:07.886 --> 00:28:09.816 what about at resting state?
NOTE Confidence: 0.731726679954545

00:28:09.820 --> 00:28:11.932 We obtained a Meg at 6 to 9
NOTE Confidence: 0.731726679954545

00:28:11.932 --> 00:28:14.153 hours after ketamine at the peak
NOTE Confidence: 0.731726679954545

00:28:14.153 --> 00:28:15.777 when antidepressant fix happened
NOTE Confidence: 0.731726679954545

00:28:15.777 --> 00:28:17.879 in the dissociative side.
NOTE Confidence: 0.731726679954545

00:28:17.880 --> 00:28:21.996 Effects of have diminished towards the top.
NOTE Confidence: 0.731726679954545

00:28:22.000 --> 00:28:24.054 You see the press subjects, the bottom.

NOTE Confidence: 0.731726679954545
00:28:24.054 --> 00:28:26.316 You see healthy controls and you
NOTE Confidence: 0.731726679954545
00:28:26.316 --> 00:28:28.740 see increases in gamma power in the
NOTE Confidence: 0.731726679954545
00:28:28.740 --> 00:28:31.379 default mode network in the triple network,
NOTE Confidence: 0.731726679954545
00:28:31.380 --> 00:28:33.468 specifically towards the right you see,
NOTE Confidence: 0.731726679954545
00:28:33.470 --> 00:28:34.286 for example,
NOTE Confidence: 0.731726679954545
00:28:34.286 --> 00:28:35.102 in green,
NOTE Confidence: 0.731726679954545
00:28:35.102 --> 00:28:37.550 the right insula increases with ketamine.
NOTE Confidence: 0.731726679954545
00:28:37.550 --> 00:28:39.920 That approaches the healthy control
NOTE Confidence: 0.731726679954545
00:28:39.920 --> 00:28:40.868 subjects baseline,
NOTE Confidence: 0.731726679954545
00:28:40.870 --> 00:28:44.388 so it suggests normalization here and
NOTE Confidence: 0.731726679954545
00:28:44.388 --> 00:28:46.656 also within the central executive network,
NOTE Confidence: 0.731726679954545
00:28:46.660 --> 00:28:48.644 so ketamine is doing a lot of things.
NOTE Confidence: 0.786572545555555
00:28:48.650 --> 00:28:52.682 But here our interest is in a triple network.
NOTE Confidence: 0.786572545555555
00:28:52.690 --> 00:28:54.925 And, importantly, that the baseline
NOTE Confidence: 0.786572545555555
00:28:54.925 --> 00:28:57.959 gamma power seems to moderate the end
NOTE Confidence: 0.786572545555555

00:28:57.959 --> 00:29:00.125 of the prison effects of ketamine.
NOTE Confidence: 0.7865725455555555

00:29:00.130 --> 00:29:02.598 The lower the gamma power, the better.
NOTE Confidence: 0.7865725455555555

00:29:02.598 --> 00:29:04.068 The antidepressant effects of ketamine.
NOTE Confidence: 0.7865725455555555

00:29:04.070 --> 00:29:07.410 The higher suggest no response
NOTE Confidence: 0.7865725455555555

00:29:07.410 --> 00:29:09.710 or even worsening subjects with
NOTE Confidence: 0.7865725455555555

00:29:09.710 --> 00:29:12.349 who are treated with Academy.
NOTE Confidence: 0.7865725455555555

00:29:12.350 --> 00:29:15.857 Now we now move into a stimulus
NOTE Confidence: 0.7865725455555555

00:29:15.857 --> 00:29:18.250 induced gamma power changes.
NOTE Confidence: 0.7865725455555555

00:29:18.250 --> 00:29:20.462 As I mentioned earlier,
NOTE Confidence: 0.7865725455555555

00:29:20.462 --> 00:29:24.608 this was earlier work where one does a
NOTE Confidence: 0.7865725455555555

00:29:24.608 --> 00:29:26.834 sensory task which you use in nomadic
NOTE Confidence: 0.7865725455555555

00:29:26.834 --> 00:29:29.072 device to stimulate the sensory cortex
NOTE Confidence: 0.7865725455555555

00:29:29.072 --> 00:29:31.791 you could see here the plastic changes
NOTE Confidence: 0.7865725455555555

00:29:31.791 --> 00:29:34.248 that occur and this is referred to
NOTE Confidence: 0.7865725455555555

00:29:34.248 --> 00:29:35.931 as stimulus induced gamma power.
NOTE Confidence: 0.7865725455555555

00:29:35.931 --> 00:29:37.566 So you select within the

NOTE Confidence: 0.786572545555555

00:29:37.566 --> 00:29:39.250 30 to 50 Hertz range.

NOTE Confidence: 0.786572545555555

00:29:39.250 --> 00:29:42.490 In an earlier study we looked at 21.

NOTE Confidence: 0.786572545555555

00:29:42.490 --> 00:29:44.101 Dedicated subjects and.

NOTE Confidence: 0.786572545555555

00:29:44.101 --> 00:29:47.323 What you find here at baseline,

NOTE Confidence: 0.786572545555555

00:29:47.330 --> 00:29:49.965 no difference between responders and

NOTE Confidence: 0.786572545555555

00:29:49.965 --> 00:29:52.349 non responders. But post ketamine.

NOTE Confidence: 0.786572545555555

00:29:52.349 --> 00:29:55.007 You see that stimulus induced gamma

NOTE Confidence: 0.786572545555555

00:29:55.007 --> 00:29:58.128 power significantly increases compared to

NOTE Confidence: 0.786572545555555

00:29:58.128 --> 00:30:00.046 baseline suggestion plasticity phenomena.

NOTE Confidence: 0.786572545555555

00:30:00.046 --> 00:30:03.399 Now we went on to replicate this in

NOTE Confidence: 0.786572545555555

00:30:03.399 --> 00:30:05.385 the control study I mentioned earlier

NOTE Confidence: 0.786572545555555

00:30:05.385 --> 00:30:08.167 and on the bottom what you see here

NOTE Confidence: 0.786572545555555

00:30:08.167 --> 00:30:10.726 are the responders using the same task

NOTE Confidence: 0.786572545555555

00:30:10.726 --> 00:30:13.234 increase in stimulus induced gamma power.

NOTE Confidence: 0.786572545555555

00:30:13.240 --> 00:30:15.420 Non responders, no changes,

NOTE Confidence: 0.786572545555555

00:30:15.420 --> 00:30:17.055 healthy control changes,
NOTE Confidence: 0.7865725455555555

00:30:17.060 --> 00:30:18.740 no changes in gamma power,
NOTE Confidence: 0.7865725455555555

00:30:18.740 --> 00:30:21.310 suggesting specificity.
NOTE Confidence: 0.7865725455555555

00:30:21.310 --> 00:30:23.165 Towards the right you see the peak,
NOTE Confidence: 0.7865725455555555

00:30:23.170 --> 00:30:24.154 gamma, ketamine,
NOTE Confidence: 0.7865725455555555

00:30:24.154 --> 00:30:26.122 placebo differences at the
NOTE Confidence: 0.7865725455555555

00:30:26.122 --> 00:30:28.090 peak of the antidepressants.
NOTE Confidence: 0.7865725455555555

00:30:28.090 --> 00:30:29.014 Effects of ketamine,
NOTE Confidence: 0.7865725455555555

00:30:29.014 --> 00:30:31.728 which is at 24 hours in a very
NOTE Confidence: 0.7865725455555555

00:30:31.728 --> 00:30:32.710 nice correlation.
NOTE Confidence: 0.7865725455555555

00:30:32.710 --> 00:30:35.710 So here we have some evidence
NOTE Confidence: 0.7865725455555555

00:30:35.710 --> 00:30:38.629 of a replication at our lab.
NOTE Confidence: 0.7865725455555555

00:30:38.630 --> 00:30:40.485 Now we're interested in more
NOTE Confidence: 0.7865725455555555

00:30:40.485 --> 00:30:41.969 in the dynamic measures,
NOTE Confidence: 0.7865725455555555

00:30:41.970 --> 00:30:43.610 and so, in this experiment,
NOTE Confidence: 0.7865725455555555

00:30:43.610 --> 00:30:45.386 18 unmedicated subjects were

NOTE Confidence: 0.786572545555555

00:30:45.386 --> 00:30:47.606 treated with ketamine or saline.

NOTE Confidence: 0.786572545555555

00:30:47.610 --> 00:30:49.638 The usual crossover design.

NOTE Confidence: 0.786572545555555

00:30:49.638 --> 00:30:52.173 We use the same task.

NOTE Confidence: 0.786572545555555

00:30:52.180 --> 00:30:55.180 Source localized gamma power using

NOTE Confidence: 0.786572545555555

00:30:55.180 --> 00:30:58.126 the pneumatic device you can see

NOTE Confidence: 0.786572545555555

00:30:58.126 --> 00:31:00.036 the changes in sensory cortex.

NOTE Confidence: 0.786572545555555

00:31:00.040 --> 00:31:02.212 Towards the bottom you can see

NOTE Confidence: 0.786572545555555

00:31:02.212 --> 00:31:04.975 Erps on the top control with

NOTE Confidence: 0.786572545555555

00:31:04.975 --> 00:31:06.820 baseline ketamine placebo.

NOTE Confidence: 0.786572545555555

00:31:06.820 --> 00:31:08.900 These are for one individual.

NOTE Confidence: 0.786572545555555

00:31:08.900 --> 00:31:11.658 In the bottom is for a patient.

NOTE Confidence: 0.786572545555555

00:31:11.660 --> 00:31:15.076 So what we used here is dynamic

NOTE Confidence: 0.786572545555555

00:31:15.076 --> 00:31:18.252 causal modeling to get at this

NOTE Confidence: 0.786572545555555

00:31:18.252 --> 00:31:19.616 excitation inhibition model,

NOTE Confidence: 0.786572545555555

00:31:19.616 --> 00:31:22.507 and it's a way of estimating and

NOTE Confidence: 0.786572545555555

00:31:22.507 --> 00:31:24.766 making inferences about coupling
NOTE Confidence: 0.7865725455555555

00:31:24.766 --> 00:31:27.126 within different brain regions.
NOTE Confidence: 0.7865725455555555

00:31:27.130 --> 00:31:29.608 But the difference here is that you
NOTE Confidence: 0.7865725455555555

00:31:29.608 --> 00:31:32.272 make a change in the experimental
NOTE Confidence: 0.7865725455555555

00:31:32.272 --> 00:31:34.300 context and the perturbation,
NOTE Confidence: 0.7865725455555555

00:31:34.300 --> 00:31:36.658 and then you measure that change.
NOTE Confidence: 0.7865725455555555

00:31:36.660 --> 00:31:39.096 So here you can see control,
NOTE Confidence: 0.7865725455555555

00:31:39.100 --> 00:31:41.648 you do a perturbation in this case.
NOTE Confidence: 0.7865725455555555

00:31:41.650 --> 00:31:44.562 Sensory task I mentioned and you measure
NOTE Confidence: 0.7865725455555555

00:31:44.562 --> 00:31:47.809 that change and you obtain what we
NOTE Confidence: 0.7865725455555555

00:31:47.809 --> 00:31:50.204 call changes in effective connectivity.
NOTE Confidence: 0.7865725455555555

00:31:50.210 --> 00:31:52.541 And keep in mind this was done
NOTE Confidence: 0.7865725455555555

00:31:52.541 --> 00:31:55.819 at 6 to 9 hours of post ketamine.
NOTE Confidence: 0.7865725455555555

00:31:55.820 --> 00:31:58.914 Going back at the micro circuit level,
NOTE Confidence: 0.7865725455555555

00:31:58.920 --> 00:32:01.836 what's interesting is you can then
NOTE Confidence: 0.7865725455555555

00:32:01.840 --> 00:32:05.950 generate based on the the the,

NOTE Confidence: 0.786572545555555

00:32:05.950 --> 00:32:09.485 the physiochemical properties of the

NOTE Confidence: 0.786572545555555

00:32:09.485 --> 00:32:13.020 channel biophysical models of AMPA.

NOTE Confidence: 0.786572545555555

00:32:13.020 --> 00:32:14.296 NMDA and GABA function.

NOTE Confidence: 0.786572545555555

00:32:14.296 --> 00:32:16.840 I'm not going to talk about that now,

NOTE Confidence: 0.786572545555555

00:32:16.840 --> 00:32:18.945 but you can generate estimates

NOTE Confidence: 0.786572545555555

00:32:18.945 --> 00:32:21.500 of how much excitation you have,

NOTE Confidence: 0.786572545555555

00:32:21.500 --> 00:32:23.360 how much inhibition you have,

NOTE Confidence: 0.786572545555555

00:32:23.360 --> 00:32:25.572 and this is what we refer to

NOTE Confidence: 0.786572545555555

00:32:25.572 --> 00:32:26.520 as regional dynamics.

NOTE Confidence: 0.786572545555555

00:32:26.520 --> 00:32:28.760 And also you can measure

NOTE Confidence: 0.786572545555555

00:32:28.760 --> 00:32:31.000 these dynamic changes in what

NOTE Confidence: 0.838011250625

00:32:31.089 --> 00:32:33.960 we call a A a geometric plane called

NOTE Confidence: 0.838011250625

00:32:33.960 --> 00:32:36.660 the trace determinant plane to to get

NOTE Confidence: 0.838011250625

00:32:36.660 --> 00:32:38.920 a sense of where do subjects move in

NOTE Confidence: 0.838011250625

00:32:38.920 --> 00:32:41.200 terms of their inhibition and excitation,

NOTE Confidence: 0.838011250625

00:32:41.200 --> 00:32:43.097 and how is that related to the
NOTE Confidence: 0.838011250625

00:32:43.097 --> 00:32:44.744 antidepressant? Effects of ketamine.
NOTE Confidence: 0.838011250625

00:32:44.744 --> 00:32:49.289 And so this is work by Eric Fagerholm at.
NOTE Confidence: 0.838011250625

00:32:49.290 --> 00:32:51.565 And UK and what you see here
NOTE Confidence: 0.838011250625

00:32:51.565 --> 00:32:53.948 towards the top left are patients.
NOTE Confidence: 0.838011250625

00:32:53.950 --> 00:32:56.834 Bottom you see controls and you see
NOTE Confidence: 0.838011250625

00:32:56.834 --> 00:32:58.816 this southwest orientation of this
NOTE Confidence: 0.838011250625

00:32:58.816 --> 00:33:00.850 plane where you have the changes
NOTE Confidence: 0.838011250625

00:33:00.850 --> 00:33:03.218 in modulus scores and the changes
NOTE Confidence: 0.838011250625

00:33:03.218 --> 00:33:05.248 in this trace determinant plane.
NOTE Confidence: 0.838011250625

00:33:05.250 --> 00:33:07.370 This is associated with response.
NOTE Confidence: 0.838011250625

00:33:07.370 --> 00:33:09.350 If you plug in the numbers.
NOTE Confidence: 0.838011250625

00:33:09.350 --> 00:33:11.210 Unfortunately this is at work,
NOTE Confidence: 0.838011250625

00:33:11.210 --> 00:33:13.710 but you have excitation excitation
NOTE Confidence: 0.838011250625

00:33:13.710 --> 00:33:14.710 and ambition.
NOTE Confidence: 0.838011250625

00:33:14.710 --> 00:33:17.132 You come up with this these estimates

NOTE Confidence: 0.838011250625

00:33:17.132 --> 00:33:19.349 and what you would find here.

NOTE Confidence: 0.838011250625

00:33:19.350 --> 00:33:20.410 This movie doesn't work.

NOTE Confidence: 0.838011250625

00:33:20.410 --> 00:33:22.754 Is that as you go through the different

NOTE Confidence: 0.838011250625

00:33:22.754 --> 00:33:24.494 subjects at the different times,

NOTE Confidence: 0.838011250625

00:33:24.500 --> 00:33:26.612 you find a change in excitation

NOTE Confidence: 0.838011250625

00:33:26.612 --> 00:33:29.041 ambition and subjects move to the

NOTE Confidence: 0.838011250625

00:33:29.041 --> 00:33:30.957 southwest direction that's associated

NOTE Confidence: 0.838011250625

00:33:30.957 --> 00:33:32.873 more with antidepressant response.

NOTE Confidence: 0.838011250625

00:33:32.880 --> 00:33:34.712 This now is available online if you want

NOTE Confidence: 0.838011250625

00:33:34.712 --> 00:33:36.940 to plug in your numbers and see if it works.

NOTE Confidence: 0.838011250625

00:33:36.940 --> 00:33:39.880 We're looking for replication.

NOTE Confidence: 0.838011250625

00:33:39.880 --> 00:33:41.340 Right, let's see, oh, sorry,

NOTE Confidence: 0.838011250625

00:33:41.340 --> 00:33:44.875 now the next is I talked to you about

NOTE Confidence: 0.838011250625

00:33:44.875 --> 00:33:47.740 the six to 9 hours of gamma power, right?

NOTE Confidence: 0.838011250625

00:33:47.740 --> 00:33:49.420 That probably represents

NOTE Confidence: 0.838011250625

00:33:49.420 --> 00:33:51.684 non NMDA AMPA throughput,
NOTE Confidence: 0.838011250625

00:33:51.684 --> 00:33:52.828 cortical excitability.
NOTE Confidence: 0.838011250625

00:33:52.828 --> 00:33:55.330 So, how early do the change
NOTE Confidence: 0.838011250625

00:33:55.330 --> 00:33:56.874 of gamma power happen?
NOTE Confidence: 0.838011250625

00:33:56.880 --> 00:33:58.136 We know glutamate changes
NOTE Confidence: 0.838011250625

00:33:58.136 --> 00:33:59.706 may happen in 15 minutes,
NOTE Confidence: 0.838011250625

00:33:59.710 --> 00:34:01.132 and so this is a question
NOTE Confidence: 0.838011250625

00:34:01.132 --> 00:34:02.080 we've been looking at.
NOTE Confidence: 0.838011250625

00:34:02.080 --> 00:34:04.408 The new Barrett and the New Barrett study
NOTE Confidence: 0.838011250625

00:34:04.408 --> 00:34:06.618 where we are doing measures of fMRI,
NOTE Confidence: 0.838011250625

00:34:06.620 --> 00:34:08.172 EEG, and the scanner,
NOTE Confidence: 0.838011250625

00:34:08.172 --> 00:34:09.336 and also MG.
NOTE Confidence: 0.838011250625

00:34:09.340 --> 00:34:11.386 And looking at these different tools.
NOTE Confidence: 0.838011250625

00:34:11.390 --> 00:34:13.329 So here using the same task as,
NOTE Confidence: 0.838011250625

00:34:13.330 --> 00:34:16.090 this is a different sample.
NOTE Confidence: 0.838011250625

00:34:16.090 --> 00:34:17.766 Some matters sensory cortex.

NOTE Confidence: 0.838011250625

00:34:17.766 --> 00:34:20.280 We see changes in gamma power

NOTE Confidence: 0.838011250625

00:34:20.357 --> 00:34:22.545 almost immediately with ketamine

NOTE Confidence: 0.838011250625

00:34:22.545 --> 00:34:25.350 during the infusion, 6 to 9 hours.

NOTE Confidence: 0.838011250625

00:34:25.350 --> 00:34:26.510 It seems to increase.

NOTE Confidence: 0.838011250625

00:34:26.510 --> 00:34:28.010 Again, this is very preliminary.

NOTE Confidence: 0.838011250625

00:34:28.010 --> 00:34:29.389 We have to look at the data.

NOTE Confidence: 0.838011250625

00:34:29.390 --> 00:34:31.475 No significant changes in the

NOTE Confidence: 0.838011250625

00:34:31.475 --> 00:34:33.143 placebo or saline condition.

NOTE Confidence: 0.838011250625

00:34:33.150 --> 00:34:35.058 So so just that there's something

NOTE Confidence: 0.838011250625

00:34:35.058 --> 00:34:36.570 going on very early on,

NOTE Confidence: 0.838011250625

00:34:36.570 --> 00:34:39.408 maybe consistent with the glutamate burst.

NOTE Confidence: 0.838011250625

00:34:39.410 --> 00:34:42.763 Now earlier work to get it plasticity

NOTE Confidence: 0.838011250625

00:34:42.763 --> 00:34:45.070 potentiation because if we believe

NOTE Confidence: 0.838011250625

00:34:45.070 --> 00:34:48.094 that there's a glutamate burst and

NOTE Confidence: 0.838011250625

00:34:48.094 --> 00:34:50.518 activation suggest plasticity is that

NOTE Confidence: 0.838011250625

00:34:50.518 --> 00:34:53.126 we we did a study and published it
NOTE Confidence: 0.838011250625

00:34:53.130 --> 00:34:56.592 probably some time back where Julia
NOTE Confidence: 0.838011250625

00:34:56.592 --> 00:34:59.468 Tononi what he noticed was that if
NOTE Confidence: 0.838011250625

00:34:59.468 --> 00:35:02.652 you do a new visual motor task here,
NOTE Confidence: 0.838011250625

00:35:02.660 --> 00:35:04.028 the person sitting on the computer,
NOTE Confidence: 0.838011250625

00:35:04.030 --> 00:35:05.410 something not previously learned
NOTE Confidence: 0.838011250625

00:35:05.410 --> 00:35:07.984 what you find at night is increasing
NOTE Confidence: 0.838011250625

00:35:07.984 --> 00:35:10.169 the slow wave activity precisely.
NOTE Confidence: 0.838011250625

00:35:10.170 --> 00:35:12.452 In the area of the motor changes
NOTE Confidence: 0.838011250625

00:35:12.452 --> 00:35:14.494 and suggest that they're probably
NOTE Confidence: 0.838011250625

00:35:14.494 --> 00:35:16.490 plasticity changes going on,
NOTE Confidence: 0.838011250625

00:35:16.490 --> 00:35:18.429 so in collaboration with them we did.
NOTE Confidence: 0.838011250625

00:35:18.430 --> 00:35:19.638 We wondered whether ketamine
NOTE Confidence: 0.838011250625

00:35:19.638 --> 00:35:21.148 might be involved in this.
NOTE Confidence: 0.838011250625

00:35:21.150 --> 00:35:23.946 Could this be a putative marker
NOTE Confidence: 0.838011250625

00:35:23.946 --> 00:35:25.344 of synaptic potentiation?

NOTE Confidence: 0.838011250625

00:35:25.350 --> 00:35:29.180 The simple cartoon here is that in

NOTE Confidence: 0.838011250625

00:35:29.180 --> 00:35:32.033 responders you would have in AMP

NOTE Confidence: 0.838011250625

00:35:32.033 --> 00:35:34.589 insertions and haptic potentiation.

NOTE Confidence: 0.838011250625

00:35:34.590 --> 00:35:37.264 In Nonresponders there would be no insertion,

NOTE Confidence: 0.838011250625

00:35:37.270 --> 00:35:38.614 no seductive potentiation,

NOTE Confidence: 0.838011250625

00:35:38.614 --> 00:35:39.062 so.

NOTE Confidence: 0.838011250625

00:35:39.062 --> 00:35:41.750 Early work in rodents suggests that

NOTE Confidence: 0.838011250625

00:35:41.821 --> 00:35:44.196 when you give ketamine injections

NOTE Confidence: 0.838011250625

00:35:44.196 --> 00:35:46.096 and medial prefrontal cortex,

NOTE Confidence: 0.869901126666667

00:35:46.100 --> 00:35:49.310 you find increases in synaptic strength.

NOTE Confidence: 0.869901126666667

00:35:49.310 --> 00:35:50.830 And you also find increase

NOTE Confidence: 0.869901126666667

00:35:50.830 --> 00:35:52.046 in slow wave sleep.

NOTE Confidence: 0.869901126666667

00:35:52.050 --> 00:35:56.180 That's delta between 0 and 40 Hertz.

NOTE Confidence: 0.869901126666667

00:35:56.180 --> 00:35:57.672 So we wondered whether

NOTE Confidence: 0.869901126666667

00:35:57.672 --> 00:35:59.537 this also occurs in humans,

NOTE Confidence: 0.869901126666667

00:35:59.540 --> 00:36:02.858 and so in a previous publication,
NOTE Confidence: 0.869901126666667

00:36:02.860 --> 00:36:05.492 this looks at changes in slow wave
NOTE Confidence: 0.869901126666667

00:36:05.492 --> 00:36:08.716 sleep in the first cycle you see
NOTE Confidence: 0.869901126666667

00:36:08.716 --> 00:36:11.236 significant increases with ketamine and
NOTE Confidence: 0.869901126666667

00:36:11.236 --> 00:36:14.538 red compared to the baseline and blue.
NOTE Confidence: 0.869901126666667

00:36:14.540 --> 00:36:18.041 And so we have in in the earlier work
NOTE Confidence: 0.869901126666667

00:36:18.041 --> 00:36:21.808 what we found as a relationship that
NOTE Confidence: 0.869901126666667

00:36:21.808 --> 00:36:24.830 responders to ketamine seem to have.
NOTE Confidence: 0.869901126666667

00:36:24.830 --> 00:36:26.750 Increases in slow activity
NOTE Confidence: 0.869901126666667

00:36:26.750 --> 00:36:28.670 compared to non responders.
NOTE Confidence: 0.869901126666667

00:36:28.670 --> 00:36:30.742 It's taken us a while but we've been
NOTE Confidence: 0.869901126666667

00:36:30.742 --> 00:36:33.191 able to to look at and subsequently
NOTE Confidence: 0.869901126666667

00:36:33.191 --> 00:36:34.683 replicate this just recently.
NOTE Confidence: 0.869901126666667

00:36:34.690 --> 00:36:35.878 So Torres are right.
NOTE Confidence: 0.869901126666667

00:36:35.878 --> 00:36:38.250 If you look at healthy control subjects,
NOTE Confidence: 0.869901126666667

00:36:38.250 --> 00:36:40.788 what you see this is SWA slow wave activity.

NOTE Confidence: 0.869901126666667

00:36:40.790 --> 00:36:43.382 What we know is that through the three

NOTE Confidence: 0.869901126666667

00:36:43.382 --> 00:36:45.989 cycles it tends to diminish over time.

NOTE Confidence: 0.869901126666667

00:36:45.990 --> 00:36:46.977 This is normal,

NOTE Confidence: 0.869901126666667

00:36:46.977 --> 00:36:48.622 but somehow if you look

NOTE Confidence: 0.869901126666667

00:36:48.622 --> 00:36:50.570 towards the depressed subjects,

NOTE Confidence: 0.869901126666667

00:36:50.570 --> 00:36:52.610 what you find is that this is disrupted.

NOTE Confidence: 0.869901126666667

00:36:52.610 --> 00:36:54.010 They don't have this normal

NOTE Confidence: 0.869901126666667

00:36:54.010 --> 00:36:54.850 pattern as healthy.

NOTE Confidence: 0.869901126666667

00:36:54.850 --> 00:36:56.620 Control subjects and in the next

NOTE Confidence: 0.869901126666667

00:36:56.620 --> 00:36:58.319 slide which you see is here,

NOTE Confidence: 0.869901126666667

00:36:58.320 --> 00:37:00.282 they're grouped up in green is

NOTE Confidence: 0.869901126666667

00:37:00.282 --> 00:37:02.319 healthy volunteers and the red or

NOTE Confidence: 0.869901126666667

00:37:02.319 --> 00:37:03.984 orange is the treatment resistant

NOTE Confidence: 0.869901126666667

00:37:03.984 --> 00:37:05.827 depression and we see you know

NOTE Confidence: 0.869901126666667

00:37:05.827 --> 00:37:07.393 that what I just showed you,

NOTE Confidence: 0.869901126666667

00:37:07.400 --> 00:37:09.370 the decrease in the healthy
NOTE Confidence: 0.869901126666667

00:37:09.370 --> 00:37:11.782 control and it's disrupted in in
NOTE Confidence: 0.869901126666667

00:37:11.782 --> 00:37:14.170 the depressed subjects towards the
NOTE Confidence: 0.869901126666667

00:37:14.170 --> 00:37:17.125 right after ketamine there this is
NOTE Confidence: 0.869901126666667

00:37:17.125 --> 00:37:18.865 no longer significantly different,
NOTE Confidence: 0.869901126666667

00:37:18.870 --> 00:37:20.814 suggesting there's normalization,
NOTE Confidence: 0.869901126666667

00:37:20.814 --> 00:37:25.360 so this pattern, it seems to normalize the.
NOTE Confidence: 0.869901126666667

00:37:25.360 --> 00:37:27.496 And put it back into play.
NOTE Confidence: 0.869901126666667

00:37:27.500 --> 00:37:30.108 Now if you look at in the next
NOTE Confidence: 0.869901126666667

00:37:30.108 --> 00:37:32.968 slide is the responders versus non
NOTE Confidence: 0.869901126666667

00:37:32.968 --> 00:37:35.618 responders towards the top left
NOTE Confidence: 0.869901126666667

00:37:35.620 --> 00:37:38.602 which you see here is that there's
NOTE Confidence: 0.869901126666667

00:37:38.602 --> 00:37:41.175 a general increase in the responders
NOTE Confidence: 0.869901126666667

00:37:41.175 --> 00:37:42.538 at 230 minutes.
NOTE Confidence: 0.869901126666667

00:37:42.538 --> 00:37:44.454 This is statistically significant
NOTE Confidence: 0.869901126666667

00:37:44.454 --> 00:37:47.141 whereas the non responders it seems

NOTE Confidence: 0.869901126666667

00:37:47.141 --> 00:37:49.253 to be flat or actually diminishes.

NOTE Confidence: 0.869901126666667

00:37:49.260 --> 00:37:52.090 So suggested that synaptic could

NOTE Confidence: 0.869901126666667

00:37:52.090 --> 00:37:54.920 potentially be a synaptic appellative.

NOTE Confidence: 0.869901126666667

00:37:54.920 --> 00:37:57.908 Markets and naptip potentiation.

NOTE Confidence: 0.869901126666667

00:37:57.910 --> 00:38:00.062 Now I'm going to skip this in the

NOTE Confidence: 0.869901126666667

00:38:00.062 --> 00:38:01.982 interest of time to get into the

NOTE Confidence: 0.869901126666667

00:38:01.982 --> 00:38:03.901 last piece of the story is that

NOTE Confidence: 0.869901126666667

00:38:03.901 --> 00:38:05.515 what would we noticed early on

NOTE Confidence: 0.869901126666667

00:38:05.515 --> 00:38:07.688 on the research unit was in.

NOTE Confidence: 0.869901126666667

00:38:07.688 --> 00:38:10.130 This is clinical observation is the

NOTE Confidence: 0.869901126666667

00:38:10.206 --> 00:38:13.006 half Life Academy is a few hours

NOTE Confidence: 0.869901126666667

00:38:13.006 --> 00:38:15.090 dissociate side effects last 40

NOTE Confidence: 0.869901126666667

00:38:15.090 --> 00:38:17.190 minutes after the infusion and but

NOTE Confidence: 0.869901126666667

00:38:17.190 --> 00:38:19.110 you you have this ongoing and at the

NOTE Confidence: 0.869901126666667

00:38:19.167 --> 00:38:20.703 present response and it fades off

NOTE Confidence: 0.869901126666667

00:38:20.703 --> 00:38:22.989 by the end of one week to two weeks.
NOTE Confidence: 0.869901126666667

00:38:22.990 --> 00:38:26.288 We really talked about so early
NOTE Confidence: 0.869901126666667

00:38:26.288 --> 00:38:28.200 on we wondered whether.
NOTE Confidence: 0.869901126666667

00:38:28.200 --> 00:38:30.790 The Academy Is actually a pro drug
NOTE Confidence: 0.869901126666667

00:38:30.790 --> 00:38:32.716 and what maybe some of the mentalists
NOTE Confidence: 0.869901126666667

00:38:32.716 --> 00:38:34.340 might be active and at a present,
NOTE Confidence: 0.869901126666667

00:38:34.340 --> 00:38:36.698 and so in collaboration with many
NOTE Confidence: 0.869901126666667

00:38:36.698 --> 00:38:38.960 tagula at University of Maryland.
NOTE Confidence: 0.869901126666667

00:38:38.960 --> 00:38:43.321 Craig Thomas at Ncats and Pat Morris
NOTE Confidence: 0.869901126666667

00:38:43.321 --> 00:38:47.400 and and ruined model and others.
NOTE Confidence: 0.869901126666667

00:38:47.400 --> 00:38:49.890 Urban Weiner but was identified
NOTE Confidence: 0.869901126666667

00:38:49.890 --> 00:38:53.490 is that we found these metabolites
NOTE Confidence: 0.869901126666667

00:38:53.490 --> 00:38:56.106 lasting 3 to 7 days and we said,
NOTE Confidence: 0.869901126666667

00:38:56.110 --> 00:38:56.404 wow,
NOTE Confidence: 0.869901126666667

00:38:56.404 --> 00:38:58.462 that's around the same time as the
NOTE Confidence: 0.869901126666667

00:38:58.462 --> 00:39:00.070 duration and personal effects,

NOTE Confidence: 0.869901126666667
00:39:00.070 --> 00:39:01.526 and we said, wow, this is interesting.
NOTE Confidence: 0.869901126666667
00:39:01.530 --> 00:39:02.427 So we went.
NOTE Confidence: 0.869901126666667
00:39:02.427 --> 00:39:04.221 What are these H&K metabolites and
NOTE Confidence: 0.869901126666667
00:39:04.221 --> 00:39:04.520 we
NOTE Confidence: 0.8085377125
00:39:04.590 --> 00:39:06.230 found disappointingly that they
NOTE Confidence: 0.8085377125
00:39:06.230 --> 00:39:08.690 were inactive when we say inactive,
NOTE Confidence: 0.8085377125
00:39:08.690 --> 00:39:10.706 that was it was inactive for
NOTE Confidence: 0.8085377125
00:39:10.706 --> 00:39:12.050 what pain and anesthesia,
NOTE Confidence: 0.8085377125
00:39:12.050 --> 00:39:14.186 but we decided to pursue that.
NOTE Confidence: 0.8085377125
00:39:14.190 --> 00:39:15.738 And it's a series of studies
NOTE Confidence: 0.8085377125
00:39:15.738 --> 00:39:17.580 that led to a candid drug.
NOTE Confidence: 0.8085377125
00:39:17.580 --> 00:39:19.188 Who are sick Sarah and Kate?
NOTE Confidence: 0.8085377125
00:39:19.190 --> 00:39:21.549 The two successive is also an antidepressant,
NOTE Confidence: 0.8085377125
00:39:21.550 --> 00:39:25.106 but we pursued this for other reasons.
NOTE Confidence: 0.8085377125
00:39:25.110 --> 00:39:26.880 To briefly summarize,
NOTE Confidence: 0.8085377125

00:39:26.880 --> 00:39:29.240 you give racemic ketamine.
NOTE Confidence: 0.8085377125

00:39:29.240 --> 00:39:31.494 And what you find is in rodents
NOTE Confidence: 0.8085377125

00:39:31.500 --> 00:39:33.340 high levels of ketamine,
NOTE Confidence: 0.8085377125

00:39:33.340 --> 00:39:37.148 and then the metabolite 2 or 6 origin K.
NOTE Confidence: 0.8085377125

00:39:37.150 --> 00:39:40.012 Through a process where you strengthen
NOTE Confidence: 0.8085377125

00:39:40.012 --> 00:39:42.342 carbon 6, you produce D2 ketamine.
NOTE Confidence: 0.8085377125

00:39:42.342 --> 00:39:44.018 You die, deteriorate, deteriorate,
NOTE Confidence: 0.8085377125

00:39:44.018 --> 00:39:46.488 ketamine when you do so.
NOTE Confidence: 0.8085377125

00:39:46.490 --> 00:39:48.062 Towards the right,
NOTE Confidence: 0.8085377125

00:39:48.062 --> 00:39:50.682 you effectively reduce or eliminate
NOTE Confidence: 0.8085377125

00:39:50.682 --> 00:39:52.649 the metabolism of Academy.
NOTE Confidence: 0.8085377125

00:39:52.650 --> 00:39:53.634 So in essence,
NOTE Confidence: 0.8085377125

00:39:53.634 --> 00:39:55.602 now you have D2 ketamine and
NOTE Confidence: 0.8085377125

00:39:55.602 --> 00:39:58.007 if you look at the bottom left,
NOTE Confidence: 0.8085377125

00:39:58.010 --> 00:40:01.016 this is the competitive binding assay.
NOTE Confidence: 0.8085377125

00:40:01.020 --> 00:40:02.970 MK 801 for an MDA receptors,

NOTE Confidence: 0.8085377125

00:40:02.970 --> 00:40:05.304 you see an overlap between D2

NOTE Confidence: 0.8085377125

00:40:05.304 --> 00:40:06.860 ketamine and racemic ketamine.

NOTE Confidence: 0.8085377125

00:40:06.860 --> 00:40:09.620 Would return retains its

NOTE Confidence: 0.8085377125

00:40:09.620 --> 00:40:11.000 pharmacological properties,

NOTE Confidence: 0.8085377125

00:40:11.000 --> 00:40:13.933 and when you test D2 ketamine it

NOTE Confidence: 0.8085377125

00:40:13.933 --> 00:40:16.777 no longer has the sustained effects

NOTE Confidence: 0.8085377125

00:40:16.777 --> 00:40:20.150 of of of of racemic Academy towards

NOTE Confidence: 0.8085377125

00:40:20.150 --> 00:40:22.880 the right we take our Canada drug

NOTE Confidence: 0.8085377125

00:40:22.880 --> 00:40:25.826 which is 2R6RH K and effective.

NOTE Confidence: 0.8085377125

00:40:25.830 --> 00:40:28.315 We see it in Nice dose relationship

NOTE Confidence: 0.8085377125

00:40:28.315 --> 00:40:30.252 with different doses and both

NOTE Confidence: 0.8085377125

00:40:30.252 --> 00:40:31.860 acute and depressive effects,

NOTE Confidence: 0.8085377125

00:40:31.860 --> 00:40:33.132 and sustained antidepressant

NOTE Confidence: 0.8085377125

00:40:33.132 --> 00:40:34.828 antidepressant effects of H&K.

NOTE Confidence: 0.763057625

00:40:37.120 --> 00:40:42.462 To to the top shows row shows that our

NOTE Confidence: 0.763057625

00:40:42.462 --> 00:40:45.358 candidate drug does not displace MK to one,
NOTE Confidence: 0.763057625

00:40:45.360 --> 00:40:48.104 so suggesting it would not have an MD
NOTE Confidence: 0.763057625

00:40:48.104 --> 00:40:51.037 and then an MDA inhibitory properties.
NOTE Confidence: 0.763057625

00:40:51.040 --> 00:40:53.242 There is no changes in prepulse
NOTE Confidence: 0.763057625

00:40:53.242 --> 00:40:55.190 inhibition and no increases in
NOTE Confidence: 0.763057625

00:40:55.190 --> 00:40:57.250 lever presses suggested there's no
NOTE Confidence: 0.763057625

00:40:57.250 --> 00:40:59.100 abuse potential towards the middle.
NOTE Confidence: 0.763057625

00:40:59.100 --> 00:41:02.094 I'm not going to go in just to summarize,
NOTE Confidence: 0.763057625

00:41:02.094 --> 00:41:04.320 when you give and be QX and
NOTE Confidence: 0.763057625

00:41:04.393 --> 00:41:06.398 AMP and antagonist you block.
NOTE Confidence: 0.763057625

00:41:06.400 --> 00:41:09.060 Canada person effects not only have ketamine,
NOTE Confidence: 0.763057625

00:41:09.060 --> 00:41:10.730 but of our Canada drug.
NOTE Confidence: 0.763057625

00:41:10.730 --> 00:41:12.990 H&K suggests an AMP activation
NOTE Confidence: 0.763057625

00:41:12.990 --> 00:41:14.346 throughput is important.
NOTE Confidence: 0.763057625

00:41:14.350 --> 00:41:16.580 Towards the bottom we see
NOTE Confidence: 0.763057625

00:41:16.580 --> 00:41:18.364 increases in gamma power.

NOTE Confidence: 0.763057625

00:41:18.370 --> 00:41:21.718 Towards the left you see the the changes in

NOTE Confidence: 0.763057625

00:41:21.718 --> 00:41:24.967 gamma with racemic ketamine also with 2R6R18

NOTE Confidence: 0.763057625

00:41:24.967 --> 00:41:28.096 Care Canada drug and towards the right.

NOTE Confidence: 0.763057625

00:41:28.100 --> 00:41:30.120 We see the figure showing

NOTE Confidence: 0.763057625

00:41:30.120 --> 00:41:32.680 increases in green of gamma power,

NOTE Confidence: 0.763057625

00:41:32.680 --> 00:41:36.257 but it's blocked with pretreatment with NBQX,

NOTE Confidence: 0.763057625

00:41:36.257 --> 00:41:37.531 so again,

NOTE Confidence: 0.763057625

00:41:37.531 --> 00:41:40.079 suggesting a potential biomarker.

NOTE Confidence: 0.763057625

00:41:40.080 --> 00:41:42.495 To summarize this part of the story

NOTE Confidence: 0.763057625

00:41:42.495 --> 00:41:44.840 of a cartoon you give ketamine,

NOTE Confidence: 0.763057625

00:41:44.840 --> 00:41:47.480 racemic, ketamine within minutes.

NOTE Confidence: 0.763057625

00:41:47.480 --> 00:41:50.780 You have two dozen metabolites.

NOTE Confidence: 0.763057625

00:41:50.780 --> 00:41:52.436 Some of them we could argue

NOTE Confidence: 0.763057625

00:41:52.436 --> 00:41:54.130 involved in side effects addiction,

NOTE Confidence: 0.763057625

00:41:54.130 --> 00:41:56.230 others in the rapid antidepressant effects.

NOTE Confidence: 0.763057625

00:41:56.230 --> 00:41:57.790 How do we separate them?
NOTE Confidence: 0.763057625

00:41:57.790 --> 00:42:00.494 We do so by process called we do
NOTE Confidence: 0.763057625

00:42:00.494 --> 00:42:02.870 turate carbon 6 strength and carbon.
NOTE Confidence: 0.763057625

00:42:02.870 --> 00:42:05.015 You effectively reduce or eliminate
NOTE Confidence: 0.763057625

00:42:05.015 --> 00:42:07.582 or block the metabolism we take
NOTE Confidence: 0.763057625

00:42:07.582 --> 00:42:09.694 our create new newly created drug
NOTE Confidence: 0.763057625

00:42:09.694 --> 00:42:12.250 which is the same as racemic
NOTE Confidence: 0.763057625

00:42:12.250 --> 00:42:14.146 ketamine without the metabolism.
NOTE Confidence: 0.763057625

00:42:14.150 --> 00:42:15.949 The two ketamine when we do so
NOTE Confidence: 0.763057625

00:42:15.949 --> 00:42:17.823 it doesn't have the sustained and
NOTE Confidence: 0.763057625

00:42:17.823 --> 00:42:19.568 the present effects of ketamine,
NOTE Confidence: 0.763057625

00:42:19.570 --> 00:42:20.986 but still has a side effects.
NOTE Confidence: 0.763057625

00:42:20.990 --> 00:42:23.090 But side effects in addiction,
NOTE Confidence: 0.763057625

00:42:23.090 --> 00:42:23.926 addictive properties,
NOTE Confidence: 0.763057625

00:42:23.926 --> 00:42:27.490 we take our candidate drug to our six R.
NOTE Confidence: 0.763057625

00:42:27.490 --> 00:42:28.970 We inject it in rodents.

NOTE Confidence: 0.763057625

00:42:28.970 --> 00:42:30.710 It's not an MD antagonist.

NOTE Confidence: 0.763057625

00:42:30.710 --> 00:42:32.576 At physiological concentrations

NOTE Confidence: 0.763057625

00:42:32.576 --> 00:42:35.686 it doesn't have abuse potential,

NOTE Confidence: 0.763057625

00:42:35.690 --> 00:42:38.219 it activates AMPA.

NOTE Confidence: 0.763057625

00:42:38.220 --> 00:42:39.144 And it says we,

NOTE Confidence: 0.763057625

00:42:39.144 --> 00:42:40.530 in essence we separate the wheat

NOTE Confidence: 0.763057625

00:42:40.578 --> 00:42:41.298 from the chaff.

NOTE Confidence: 0.763057625

00:42:41.300 --> 00:42:45.017 I think I have about a few minutes left.

NOTE Confidence: 0.763057625

00:42:45.020 --> 00:42:48.940 We've done some deconvolution

NOTE Confidence: 0.763057625

00:42:48.940 --> 00:42:50.900 studies deconstructed.

NOTE Confidence: 0.763057625

00:42:50.900 --> 00:42:51.960 To our six Origin key,

NOTE Confidence: 0.763057625

00:42:51.960 --> 00:42:53.690 this is unpublished work and

NOTE Confidence: 0.763057625

00:42:53.690 --> 00:42:55.961 what we can summarize here using

NOTE Confidence: 0.763057625

00:42:55.961 --> 00:42:57.377 the competitive binding.

NOTE Confidence: 0.763057625

00:42:57.380 --> 00:42:59.900 Radio login assays is that

NOTE Confidence: 0.763057625

00:42:59.900 --> 00:43:02.420 it doesn't inhibit an NDA.
NOTE Confidence: 0.763057625

00:43:02.420 --> 00:43:05.143 It doesn't have effects on new opioid
NOTE Confidence: 0.763057625

00:43:05.143 --> 00:43:07.519 receptors or capital opioid receptors.
NOTE Confidence: 0.763057625

00:43:07.520 --> 00:43:11.760 When we do FDG PET imaging of rodents
NOTE Confidence: 0.763057625

00:43:11.760 --> 00:43:15.080 treated with saline or 2R6RH and K,
NOTE Confidence: 0.763057625

00:43:15.080 --> 00:43:17.880 you see that it does increase insulin
NOTE Confidence: 0.763057625

00:43:17.960 --> 00:43:19.640 activity, metabolic activity,
NOTE Confidence: 0.763057625

00:43:19.640 --> 00:43:21.472 and insular nucleus. Combines.
NOTE Confidence: 0.763057625

00:43:21.472 --> 00:43:23.432 Towards the bottom right or
NOTE Confidence: 0.763057625

00:43:23.432 --> 00:43:25.800 matrices you see the changes with
NOTE Confidence: 0.763057625

00:43:25.800 --> 00:43:28.355 Esketamine to our six RHK has a
NOTE Confidence: 0.763057625

00:43:28.355 --> 00:43:30.477 different pattern than as ketamine,
NOTE Confidence: 0.763057625

00:43:30.480 --> 00:43:33.918 suggesting that these are different drugs.
NOTE Confidence: 0.763057625

00:43:33.920 --> 00:43:37.358 To summarize what I'm going to move on to,
NOTE Confidence: 0.763057625

00:43:37.360 --> 00:43:40.608 the last couple slides.
NOTE Confidence: 0.763057625

00:43:40.610 --> 00:43:42.770 Ketamine has different potential

NOTE Confidence: 0.763057625

00:43:42.770 --> 00:43:44.930 theories on its mechanism.

NOTE Confidence: 0.763057625

00:43:44.930 --> 00:43:47.138 Blocking extrasynaptic receptors,

NOTE Confidence: 0.763057625

00:43:47.138 --> 00:43:49.346 synaptic NMDA receptors,

NOTE Confidence: 0.763057625

00:43:49.350 --> 00:43:51.482 Gabaergic and NMDA receptors,

NOTE Confidence: 0.763057625

00:43:51.482 --> 00:43:54.147 and Gabaergic interneurons with the

NOTE Confidence: 0.763057625

00:43:54.147 --> 00:43:56.777 glutamate burst or metabolism through

NOTE Confidence: 0.763057625

00:43:56.777 --> 00:43:59.302 liver producing hydroxy nor ketamine

NOTE Confidence: 0.763057625

00:43:59.310 --> 00:44:02.448 and increase in release of glutamate.

NOTE Confidence: 0.763057625

00:44:02.450 --> 00:44:04.590 AMPA activation downstream changes

NOTE Confidence: 0.763057625

00:44:04.590 --> 00:44:08.353 I already showed you the changes in

NOTE Confidence: 0.763057625

00:44:08.353 --> 00:44:11.058 gamma power in preclinical studies.

NOTE Confidence: 0.763057625

00:44:11.060 --> 00:44:13.568 In a recent study we looked

NOTE Confidence: 0.763057625

00:44:13.568 --> 00:44:15.240 at the combined 2

NOTE Confidence: 0.771064133125

00:44:15.336 --> 00:44:17.658 success to our six R 18K.

NOTE Confidence: 0.771064133125

00:44:17.660 --> 00:44:19.781 In in our subjects and we find

NOTE Confidence: 0.771064133125

00:44:19.781 --> 00:44:21.130 increases in gamma power.
NOTE Confidence: 0.771064133125

00:44:21.130 --> 00:44:24.506 So suggesting that the changes also might
NOTE Confidence: 0.771064133125

00:44:24.506 --> 00:44:27.734 be relevant to developing the drug.
NOTE Confidence: 0.771064133125

00:44:27.740 --> 00:44:29.795 Just recently completed is a
NOTE Confidence: 0.771064133125

00:44:29.795 --> 00:44:32.240 study where we looked at CSF,
NOTE Confidence: 0.771064133125

00:44:32.240 --> 00:44:35.456 plasma and CSF for 28 hours,
NOTE Confidence: 0.771064133125

00:44:35.460 --> 00:44:37.775 paid in in healthy volunteers
NOTE Confidence: 0.771064133125

00:44:37.775 --> 00:44:39.164 who received ketamine.
NOTE Confidence: 0.771064133125

00:44:39.170 --> 00:44:42.968 They had the MG and what you find here.
NOTE Confidence: 0.771064133125

00:44:42.970 --> 00:44:44.114 There's a bottom left.
NOTE Confidence: 0.771064133125

00:44:44.114 --> 00:44:46.110 You could see the changes in 2R6,
NOTE Confidence: 0.771064133125

00:44:46.110 --> 00:44:47.606 R and two success.
NOTE Confidence: 0.771064133125

00:44:47.606 --> 00:44:50.392 We see greater the area under the
NOTE Confidence: 0.771064133125

00:44:50.392 --> 00:44:52.667 curve for CSF is significantly,
NOTE Confidence: 0.771064133125

00:44:52.670 --> 00:44:55.001 however, to our six R compared to
NOTE Confidence: 0.771064133125

00:44:55.001 --> 00:44:57.387 two as success and also in plasma.

NOTE Confidence: 0.771064133125

00:44:57.390 --> 00:44:59.410 Here are the ratios though.

NOTE Confidence: 0.771064133125

00:44:59.410 --> 00:45:02.026 The figure on the right shows

NOTE Confidence: 0.771064133125

00:45:02.026 --> 00:45:03.770 you that over time,

NOTE Confidence: 0.771064133125

00:45:03.770 --> 00:45:05.494 the changes in metabolite

NOTE Confidence: 0.771064133125

00:45:05.494 --> 00:45:08.453 levels we can see here the 230.

NOTE Confidence: 0.771064133125

00:45:08.453 --> 00:45:11.064 A minute time point we see that

NOTE Confidence: 0.771064133125

00:45:11.064 --> 00:45:13.150 they start to diverge where

NOTE Confidence: 0.771064133125

00:45:13.150 --> 00:45:15.235 two or six are increases,

NOTE Confidence: 0.771064133125

00:45:15.240 --> 00:45:19.440 2 success decreases in both CSF and plasma,

NOTE Confidence: 0.771064133125

00:45:19.440 --> 00:45:21.405 whereas it remains relatively flat

NOTE Confidence: 0.771064133125

00:45:21.405 --> 00:45:24.264 for it nor ketamine, and for ketamine.

NOTE Confidence: 0.771064133125

00:45:24.264 --> 00:45:25.976 It drops very dramatically,

NOTE Confidence: 0.771064133125

00:45:25.980 --> 00:45:27.508 suggesting well what's really

NOTE Confidence: 0.771064133125

00:45:27.508 --> 00:45:29.418 the the key player here.

NOTE Confidence: 0.771064133125

00:45:29.420 --> 00:45:31.028 I'm not going to show you

NOTE Confidence: 0.771064133125

00:45:31.028 --> 00:45:33.002 the Meg data very recently,
NOTE Confidence: 0.771064133125

00:45:33.002 --> 00:45:35.907 a paper published by Vasiliy
NOTE Confidence: 0.771064133125

00:45:35.907 --> 00:45:38.920 Kotula and Mitul Mehta's lab.
NOTE Confidence: 0.771064133125

00:45:38.920 --> 00:45:41.470 Looked at reward processing and
NOTE Confidence: 0.771064133125

00:45:41.470 --> 00:45:44.020 remitted depressed subjects and gave
NOTE Confidence: 0.771064133125

00:45:44.100 --> 00:45:46.354 ketamine in the point of this is
NOTE Confidence: 0.771064133125

00:45:46.354 --> 00:45:49.157 so you can study reward processing
NOTE Confidence: 0.771064133125

00:45:49.157 --> 00:45:51.356 changes without being influenced by
NOTE Confidence: 0.771064133125

00:45:51.356 --> 00:45:52.724 improvement in depressive symptoms.
NOTE Confidence: 0.771064133125

00:45:52.730 --> 00:45:56.426 A pretty clever study and this is
NOTE Confidence: 0.771064133125

00:45:56.426 --> 00:45:59.149 the monetary incentive delay task.
NOTE Confidence: 0.771064133125

00:45:59.150 --> 00:45:59.836 We have.
NOTE Confidence: 0.771064133125

00:45:59.836 --> 00:46:00.522 Low winds,
NOTE Confidence: 0.771064133125

00:46:00.522 --> 00:46:02.580 high winds and neutral winds and
NOTE Confidence: 0.771064133125

00:46:02.656 --> 00:46:05.296 what you find here is the greater the
NOTE Confidence: 0.771064133125

00:46:05.296 --> 00:46:07.550 activity and ventral tegmental area.

NOTE Confidence: 0.771064133125

00:46:07.550 --> 00:46:08.678 The the the.

NOTE Confidence: 0.771064133125

00:46:08.678 --> 00:46:10.934 With a positive relationship with the

NOTE Confidence: 0.771064133125

00:46:10.934 --> 00:46:12.825 metabolites who are six RH and Kane,

NOTE Confidence: 0.771064133125

00:46:12.830 --> 00:46:15.512 their study but not with the

NOTE Confidence: 0.771064133125

00:46:15.512 --> 00:46:16.406 other metabolite,

NOTE Confidence: 0.771064133125

00:46:16.410 --> 00:46:18.600 so suggesting that there's a

NOTE Confidence: 0.771064133125

00:46:18.600 --> 00:46:20.790 potential other biomarker that could

NOTE Confidence: 0.771064133125

00:46:20.866 --> 00:46:22.726 be used and suggest that perhaps

NOTE Confidence: 0.771064133125

00:46:22.726 --> 00:46:25.479 to our six or eight and K might

NOTE Confidence: 0.771064133125

00:46:25.479 --> 00:46:27.279 be a promising candidate drug.

NOTE Confidence: 0.771064133125

00:46:27.280 --> 00:46:29.840 And I might have time for nothing else,

NOTE Confidence: 0.771064133125

00:46:29.840 --> 00:46:31.292 right? I think so.

NOTE Confidence: 0.771064133125

00:46:31.292 --> 00:46:34.391 Just to show you this was this

NOTE Confidence: 0.771064133125

00:46:34.391 --> 00:46:37.720 is the last data. That we have.

NOTE Confidence: 0.771064133125

00:46:37.720 --> 00:46:39.943 It's under review where we look.

NOTE Confidence: 0.771064133125

00:46:39.943 --> 00:46:42.109 We did a metabolomic analysis of
NOTE Confidence: 0.771064133125

00:46:42.109 --> 00:46:44.963 the plasma and CSF in our healthy
NOTE Confidence: 0.771064133125

00:46:44.963 --> 00:46:47.029 volunteers who received the 40
NOTE Confidence: 0.771064133125

00:46:47.029 --> 00:46:48.904 minute infusion in a parallel
NOTE Confidence: 0.771064133125

00:46:48.904 --> 00:46:52.222 study by tag looking at a plasma
NOTE Confidence: 0.771064133125

00:46:52.222 --> 00:46:55.404 hippocampus and and looking at
NOTE Confidence: 0.771064133125

00:46:55.404 --> 00:46:58.400 either ketamine or to our 614K.
NOTE Confidence: 0.771064133125

00:46:58.400 --> 00:47:00.780 What you find in red are the
NOTE Confidence: 0.771064133125

00:47:00.873 --> 00:47:03.694 humans and in yellow are the mice.
NOTE Confidence: 0.771064133125

00:47:03.700 --> 00:47:05.600 But to summarize why ketamine
NOTE Confidence: 0.771064133125

00:47:05.600 --> 00:47:07.120 has brought therapeutic effects?
NOTE Confidence: 0.771064133125

00:47:07.120 --> 00:47:08.082 Don't know,
NOTE Confidence: 0.771064133125

00:47:08.082 --> 00:47:11.449 but you can see here by metabolomic
NOTE Confidence: 0.771064133125

00:47:11.449 --> 00:47:13.318 changes that there are changes.
NOTE Confidence: 0.771064133125

00:47:13.318 --> 00:47:16.187 In many systems, nitric oxide signaling,
NOTE Confidence: 0.771064133125

00:47:16.187 --> 00:47:16.796 mitochondria,

NOTE Confidence: 0.771064133125
00:47:16.796 --> 00:47:19.232 oxidative capacity and tour
NOTE Confidence: 0.771064133125
00:47:19.232 --> 00:47:20.450 cholesterol metabolism.
NOTE Confidence: 0.771064133125
00:47:20.450 --> 00:47:21.530 Bile acids,
NOTE Confidence: 0.771064133125
00:47:21.530 --> 00:47:24.230 which also have effects as
NOTE Confidence: 0.771064133125
00:47:24.230 --> 00:47:25.850 neurotransmitters and inflammation,
NOTE Confidence: 0.771064133125
00:47:25.850 --> 00:47:28.930 changes in kind learning pathway.
NOTE Confidence: 0.771064133125
00:47:28.930 --> 00:47:29.456 Nam,
NOTE Confidence: 0.771064133125
00:47:29.456 --> 00:47:33.664 and then ceramide pathways of will as well.
NOTE Confidence: 0.771064133125
00:47:33.670 --> 00:47:35.370 So these are potentially could
NOTE Confidence: 0.771064133125
00:47:35.370 --> 00:47:37.656 explain in part why it has
NOTE Confidence: 0.771064133125
00:47:37.656 --> 00:47:39.198 brought therapeutic effects.
NOTE Confidence: 0.771064133125
00:47:39.200 --> 00:47:40.262 And to summarize,
NOTE Confidence: 0.771064133125
00:47:40.262 --> 00:47:43.660 this is some of the ongoing work we're doing.
NOTE Confidence: 0.771064133125
00:47:43.660 --> 00:47:47.116 We're testing and do our to our antagonist.
NOTE Confidence: 0.851100288
00:47:47.120 --> 00:47:48.878 We, with Taisho, we have finished
NOTE Confidence: 0.851100288

00:47:48.878 --> 00:47:50.962 phase one and the study is going
NOTE Confidence: 0.851100288

00:47:50.962 --> 00:47:52.936 on right now in our research unit.
NOTE Confidence: 0.851100288

00:47:52.940 --> 00:47:56.300 It's an indoor 2-3 antagonist.
NOTE Confidence: 0.851100288

00:47:56.300 --> 00:47:59.000 We have completed single ascending
NOTE Confidence: 0.851100288

00:47:59.000 --> 00:48:02.070 dose of of H&K and started we'll
NOTE Confidence: 0.851100288

00:48:02.070 --> 00:48:04.060 start multiple ascending dose and
NOTE Confidence: 0.851100288

00:48:04.133 --> 00:48:07.051 hopefully in the first quarter of 2023.
NOTE Confidence: 0.851100288

00:48:07.051 --> 00:48:10.306 Tested and TRD. To summarize.
NOTE Confidence: 0.851100288

00:48:10.310 --> 00:48:12.368 We obtain information at many levels.
NOTE Confidence: 0.851100288

00:48:12.370 --> 00:48:13.460 Molecular cellular.
NOTE Confidence: 0.851100288

00:48:13.460 --> 00:48:15.640 We collaborate with our
NOTE Confidence: 0.851100288

00:48:15.640 --> 00:48:16.730 extramural colleagues,
NOTE Confidence: 0.851100288

00:48:16.730 --> 00:48:18.620 give them information they give
NOTE Confidence: 0.851100288

00:48:18.620 --> 00:48:20.510 us information and which helps
NOTE Confidence: 0.851100288

00:48:20.580 --> 00:48:22.230 us carry the signs forward.
NOTE Confidence: 0.851100288

00:48:22.230 --> 00:48:23.830 We obtain information at

NOTE Confidence: 0.851100288
00:48:23.830 --> 00:48:25.430 the circuit system level,
NOTE Confidence: 0.851100288
00:48:25.430 --> 00:48:27.250 obtain multimodal measures and
NOTE Confidence: 0.851100288
00:48:27.250 --> 00:48:29.483 the longitude of fashion to
NOTE Confidence: 0.851100288
00:48:29.483 --> 00:48:30.722 better understand treatment,
NOTE Confidence: 0.851100288
00:48:30.722 --> 00:48:32.787 and then hopefully the goal
NOTE Confidence: 0.851100288
00:48:32.787 --> 00:48:35.351 would be to obtain a biologically
NOTE Confidence: 0.851100288
00:48:35.351 --> 00:48:37.682 enriched subgroups so that we can
NOTE Confidence: 0.851100288
00:48:37.682 --> 00:48:39.547 have a better understanding of
NOTE Confidence: 0.851100288
00:48:39.547 --> 00:48:41.350 mechanism and pathophysiology.
NOTE Confidence: 0.851100288
00:48:41.350 --> 00:48:43.212 So I'd like to stop there and
NOTE Confidence: 0.851100288
00:48:43.212 --> 00:48:45.000 thank you for your attention.