WEBVTT

NOTE duration:"01:07:11.7000000"

NOTE recognizability:0.802

NOTE language:en-us

NOTE Confidence: 0.773990660272727

00:00:17.190 --> 00:00:18.198 Welcome, everyone.

NOTE Confidence: 0.773990660272727

00:00:18.198 --> 00:00:20.718 It's a pleasure today to

NOTE Confidence: 0.773990660272727

00:00:20.718 --> 00:00:22.710 have Alan antiseptic here.

NOTE Confidence: 0.773990660272727

00:00:22.710 --> 00:00:24.026 Alan, I think many of you know,

NOTE Confidence: 0.773990660272727

00:00:24.030 --> 00:00:26.030 is an associate professor in

NOTE Confidence: 0.773990660272727

00:00:26.030 --> 00:00:29.170 the Department of Psychiatry.

NOTE Confidence: 0.773990660272727

00:00:29.170 --> 00:00:31.180 As well as many other hats.

NOTE Confidence: 0.773990660272727

00:00:31.180 --> 00:00:34.069 And his was a really a pioneer in our

NOTE Confidence: 0.773990660272727

00:00:34.069 --> 00:00:37.096 in our community and bringing high

NOTE Confidence: 0.773990660272727

00:00:37.096 --> 00:00:39.200 resolution human Connectome Project

NOTE Confidence: 0.773990660272727

00:00:39.200 --> 00:00:42.329 style imaging to the community and

NOTE Confidence: 0.773990660272727

00:00:42.329 --> 00:00:44.646 then applying innovative computational

NOTE Confidence: 0.773990660272727

00:00:44.646 --> 00:00:48.336 strategies to analyzing these data.

NOTE Confidence: 0.773990660272727

00:00:48.340 --> 00:00:49.480 And then in more recent years,

NOTE Confidence: 0.773990660272727

00:00:49.480 --> 00:00:52.280 it started to do some some really

NOTE Confidence: 0.773990660272727

00:00:52.280 --> 00:00:54.693 exciting work in looking at the

NOTE Confidence: 0.773990660272727

00:00:54.693 --> 00:00:56.358 brain effects first of ketamine

NOTE Confidence: 0.773990660272727

00:00:56.358 --> 00:00:58.504 in his earlier work and then

NOTE Confidence: 0.773990660272727

00:00:58.504 --> 00:01:00.000 more recently of psilocybin,

NOTE Confidence: 0.773990660272727

00:01:00.000 --> 00:01:01.572 LSD and other psychedelics,

NOTE Confidence: 0.773990660272727

00:01:01.572 --> 00:01:03.537 which is the focus today.

NOTE Confidence: 0.773990660272727

00:01:03.540 --> 00:01:03.978 So Alan,

NOTE Confidence: 0.773990660272727

00:01:03.978 --> 00:01:05.292 thank you so much for being

NOTE Confidence: 0.773990660272727

00:01:05.292 --> 00:01:06.659 with us and we look forward

NOTE Confidence: 0.773990660272727

00:01:06.659 --> 00:01:07.780 to to learning from you.

NOTE Confidence: 0.692835325

00:01:09.820 --> 00:01:13.288 Thanks, Chris. Mark Gustavo.

NOTE Confidence: 0.692835325

00:01:13.290 --> 00:01:15.114 Anytime at all.

NOTE Confidence: 0.692835325

00:01:15.114 --> 00:01:17.335 It's really with this pandemic,

NOTE Confidence: 0.692835325

00:01:17.335 --> 00:01:19.680 I feel like I haven't seen you

NOTE Confidence: 0.692835325

00:01:19.754 --> 00:01:21.930 guys in forever and it's feeling

NOTE Confidence: 0.692835325

00:01:21.930 --> 00:01:23.730 more disconnected than ever,

NOTE Confidence: 0.692835325

00:01:23.730 --> 00:01:25.950 but it's it's it's really.

NOTE Confidence: 0.692835325

00:01:25.950 --> 00:01:27.765 I'm excited to tell you

NOTE Confidence: 0.692835325

00:01:27.765 --> 00:01:29.910 what we've been up to so.

NOTE Confidence: 0.692835325

00:01:29.910 --> 00:01:35.246 The the title is so let's see mapping

NOTE Confidence: 0.692835325

00:01:35.246 --> 00:01:36.694 or behavioral heterogeneity of

NOTE Confidence: 0.692835325

00:01:36.694 --> 00:01:38.180 psychedelic neurology and humans.

NOTE Confidence: 0.692835325

00:01:38.180 --> 00:01:40.916 So that's. An overly ambitious,

NOTE Confidence: 0.692835325

00:01:40.916 --> 00:01:42.364 probably not true title.

NOTE Confidence: 0.692835325

00:01:42.370 --> 00:01:43.955 So we're not quite there

NOTE Confidence: 0.692835325

00:01:43.955 --> 00:01:45.223 and this is aspirational.

NOTE Confidence: 0.692835325

00:01:45.230 --> 00:01:47.510 And So what I'd like to kind of

NOTE Confidence: 0.692835325

00:01:47.510 --> 00:01:49.630 talk about is as as Chris noted,

NOTE Confidence: 0.692835325

00:01:49.630 --> 00:01:51.640 what are the techniques and approaches

NOTE Confidence: 0.692835325

00:01:51.702 --> 00:01:53.227 we're bringing to bear towards

NOTE Confidence: 0.692835325

00:01:53.227 --> 00:01:55.382 this goal and some of the work

NOTE Confidence: 0.692835325

00:01:55.382 --> 00:01:57.349 that's been coming out of the lab.

NOTE Confidence: 0.692835325

00:01:57.350 --> 00:02:00.319 So it will be a hybrid of sort of the, the,

NOTE Confidence: 0.692835325

00:02:00.319 --> 00:02:03.010 the theme and the ethos of what we're doing,

NOTE Confidence: 0.692835325

00:02:03.010 --> 00:02:08.006 how some of the efforts in in mapping

NOTE Confidence: 0.692835325

00:02:08.006 --> 00:02:11.350 variation in clinical populations.

NOTE Confidence: 0.692835325

00:02:11.350 --> 00:02:13.770 Can be related to neuroimaging

NOTE Confidence: 0.692835325

00:02:13.770 --> 00:02:15.706 effects of pharmacological compounds

NOTE Confidence: 0.692835325

00:02:15.706 --> 00:02:18.009 with the focus on psychedelics.

NOTE Confidence: 0.692835325

00:02:18.010 --> 00:02:18.970 So that's kind of the idea,

NOTE Confidence: 0.692835325

00:02:18.970 --> 00:02:19.397 right.

NOTE Confidence: 0.692835325

00:02:19.397 --> 00:02:22.813 And so I I want to just disclose

NOTE Confidence: 0.692835325

00:02:22.813 --> 00:02:26.435 that I'm a member of the TAB

NOTE Confidence: 0.692835325

00:02:26.435 --> 00:02:29.600 Technology Advisory Board for Nemora

NOTE Confidence: 0.692835325

00:02:29.600 --> 00:02:32.376 Therapeutic Therapeutics I consult.

NOTE Confidence: 0.692835325

00:02:32.376 --> 00:02:35.057 For Gilgamesh and I just Co founded

NOTE Confidence: 0.692835325

00:02:35.057 --> 00:02:38.439 a biotech with my colleague John

NOTE Confidence: 0.692835325

00:02:38.439 --> 00:02:40.771 Murray that's called Manifest

NOTE Confidence: 0.692835325

00:02:40.771 --> 00:02:43.471 Technologies and I I say this

NOTE Confidence: 0.692835325

00:02:43.471 --> 00:02:45.506 really proudly because without the

NOTE Confidence: 0.692835325

00:02:45.510 --> 00:02:47.838 support of Yale the spin out what it

NOTE Confidence: 0.692835325

00:02:47.838 --> 00:02:50.258 would not be possible and so we're

NOTE Confidence: 0.692835325

00:02:50.258 --> 00:02:52.028 we're really excited about this

NOTE Confidence: 0.692835325

00:02:52.099 --> 00:02:54.185 work as it has this potential so.

NOTE Confidence: 0.692835325

00:02:54.190 --> 00:02:56.290 Basically the way I kind of

NOTE Confidence: 0.692835325

00:02:56.290 --> 00:02:58.190 think about the entire space.

NOTE Confidence: 0.879687514285714

00:03:00.630 --> 00:03:01.905 Neuropsychiatric mapping is

NOTE Confidence: 0.879687514285714

00:03:01.905 --> 00:03:04.455 really about the challenge and the

NOTE Confidence: 0.879687514285714

00:03:04.455 --> 00:03:06.102 opportunity in front of us, right?

NOTE Confidence: 0.879687514285714

00:03:06.102 --> 00:03:08.438 So there's two ways to think about it.

NOTE Confidence: 0.879687514285714

00:03:08.440 --> 00:03:10.636 And why has this opportunity not

NOTE Confidence: 0.879687514285714

00:03:10.636 --> 00:03:13.315 been realized in the field of brain

NOTE Confidence: 0.879687514285714

00:03:13.315 --> 00:03:15.975 behavioral health and I'll use this term

NOTE Confidence: 0.879687514285714

00:03:16.048 --> 00:03:18.806 brain behavioral health because I I I

NOTE Confidence: 0.879687514285714

00:03:18.806 --> 00:03:22.210 actually think it's important that we

NOTE Confidence: 0.879687514285714

00:03:22.210 --> 00:03:25.057 destigmatize this terminology, right.

NOTE Confidence: 0.879687514285714

00:03:25.057 --> 00:03:28.819 So it's a difficulties in regulating

NOTE Confidence: 0.879687514285714

00:03:28.819 --> 00:03:31.603 brain behavioral relationships that that

NOTE Confidence: 0.879687514285714

00:03:31.603 --> 00:03:34.859 we're after and then I'll talk about a

NOTE Confidence: 0.879687514285714

00:03:34.944 --> 00:03:37.802 framework for this quantitative and and.

NOTE Confidence: 0.879687514285714

00:03:37.802 --> 00:03:40.022 The neurobiological framework for mapping

NOTE Confidence: 0.879687514285714

00:03:40.022 --> 00:03:42.236 brain behavioral relationships with the

NOTE Confidence: 0.879687514285714

00:03:42.236 --> 00:03:44.346 assistance obviously of pharmacological or

NOTE Confidence: 0.879687514285714

00:03:44.346 --> 00:03:46.968 imaging as a key tool in order to do this,

NOTE Confidence: 0.879687514285714

00:03:46.970 --> 00:03:49.590 right. So what's the challenge?

NOTE Confidence: 0.879687514285714

00:03:49.590 --> 00:03:51.670 And so this is one of many challenges,

NOTE Confidence: 0.879687514285714

00:03:51.670 --> 00:03:53.526 but in my mind a very important one,

NOTE Confidence: 0.879687514285714

00:03:53.530 --> 00:03:55.758 right, which is heterogeneity.

NOTE Confidence: 0.879687514285714

00:03:55.758 --> 00:03:57.429 And by heterogeneity,

NOTE Confidence: 0.879687514285714

00:03:57.430 --> 00:04:00.238 I mean both within a human being over

NOTE Confidence: 0.879687514285714

00:04:00.238 --> 00:04:03.153 time and across people in relation

NOTE Confidence: 0.879687514285714

00:04:03.153 --> 00:04:05.732 to brain behavioral variation, right.

NOTE Confidence: 0.879687514285714

00:04:05.732 --> 00:04:08.826 And so this is an old problem.

NOTE Confidence: 0.879687514285714

00:04:08.830 --> 00:04:10.274 We know this, right?

NOTE Confidence: 0.879687514285714

00:04:10.274 --> 00:04:12.392 And so, but there are.

NOTE Confidence: 0.879687514285714

00:04:12.392 --> 00:04:15.640 Questions that arise because of this problem

NOTE Confidence: 0.879687514285714

00:04:15.719 --> 00:04:19.179 and the opportunity in front of us is if we.

NOTE Confidence: 0.879687514285714

00:04:19.180 --> 00:04:23.170 Have a drug like any compound.

NOTE Confidence: 0.879687514285714

00:04:23.170 --> 00:04:25.720 And psychedelics are a great example,

NOTE Confidence: 0.879687514285714

00:04:25.720 --> 00:04:26.089 right?

NOTE Confidence: 0.879687514285714

00:04:26.089 --> 00:04:28.672 How do we select the optimal person

NOTE Confidence: 0.879687514285714

00:04:28.672 --> 00:04:31.437 who will benefit from that compound?

NOTE Confidence: 0.879687514285714

00:04:31.440 --> 00:04:33.480 We don't have a principled quantitative,

NOTE Confidence: 0.879687514285714

00:04:33.480 --> 00:04:35.600 rationally guided framework for this,

NOTE Confidence: 0.879687514285714

00:04:35.600 --> 00:04:38.120 for anything in our field.

NOTE Confidence: 0.879687514285714

00:04:38.120 --> 00:04:39.680 And then in the future,

NOTE Confidence: 0.879687514285714

00:04:39.680 --> 00:04:39.932 right,

NOTE Confidence: 0.879687514285714

00:04:39.932 --> 00:04:41.696 if we do have a molecule right

NOTE Confidence: 0.879687514285714

00:04:41.696 --> 00:04:43.486 before we do not have a molecule,

NOTE Confidence: 0.879687514285714

00:04:43.490 --> 00:04:45.268 if we don't have a compound that

NOTE Confidence: 0.879687514285714

00:04:45.268 --> 00:04:46.763 crosses the blood brain barrier

NOTE Confidence: 0.879687514285714

00:04:46.763 --> 00:04:48.119 safely or any therapeutic,

NOTE Confidence: 0.879687514285714

00:04:48.120 --> 00:04:50.376 how do we develop one with

NOTE Confidence: 0.879687514285714

00:04:50.376 --> 00:04:52.300 individual precision as the goal,

NOTE Confidence: 0.879687514285714

00:04:52.300 --> 00:04:55.052 not patients versus controls,

NOTE Confidence: 0.879687514285714

00:04:55.052 --> 00:04:57.440 but individual people, right.

NOTE Confidence: 0.879687514285714

00:04:57.440 --> 00:05:00.000 So that's the opportunity as I see it,

NOTE Confidence: 0.879687514285714

00:05:00.000 --> 00:05:01.143 right and so.

NOTE Confidence: 0.879687514285714

00:05:01.143 --> 00:05:03.429 It's that how can we target

NOTE Confidence: 0.879687514285714

00:05:03.429 --> 00:05:04.800 specific people with?

NOTE Confidence: 0.879687514285714

00:05:04.800 --> 00:05:05.726 Quantitative precision.

NOTE Confidence: 0.879687514285714

00:05:05.726 --> 00:05:09.430 So this problem I see is mapping one

NOTE Confidence: 0.879687514285714

00:05:09.514 --> 00:05:11.833 to many levels of analysis, right?

NOTE Confidence: 0.879687514285714

00:05:11.833 --> 00:05:13.930 This is really what stands in front of us,

NOTE Confidence: 0.879687514285714

00:05:13.930 --> 00:05:16.882 so I don't have to tell you guys that.

NOTE Confidence: 0.879687514285714

00:05:16.890 --> 00:05:22.398 Polygenic disturbances and variants.

NOTE Confidence: 0.879687514285714

00:05:22.400 --> 00:05:26.880 Variations with rare mutations, right?

NOTE Confidence: 0.879687514285714

00:05:26.880 --> 00:05:29.250 Basically those are the two lowest

NOTE Confidence: 0.879687514285714

00:05:29.250 --> 00:05:31.230 level possibilities that our field

NOTE Confidence: 0.879687514285714

00:05:31.230 --> 00:05:33.533 is studying and how they can affect.

NOTE Confidence: 0.879687514285714

00:05:33.540 --> 00:05:36.000 Molecules, synapses and cells and the

NOTE Confidence: 0.879687514285714

00:05:36.000 --> 00:05:38.069 balance between those cells, right?

NOTE Confidence: 0.879687514285714

00:05:38.069 --> 00:05:40.214 That's that's at the very

NOTE Confidence: 0.879687514285714

00:05:40.214 --> 00:05:42.268 baseline of the problem, right?

NOTE Confidence: 0.879687514285714

00:05:42.268 --> 00:05:42.944 In turn,

NOTE Confidence: 0.879687514285714

00:05:42.944 --> 00:05:45.310 how do we take that information and

NOTE Confidence: 0.879687514285714

00:05:45.383 --> 00:05:47.837 map it onto system level observation?

NOTE Confidence: 0.879687514285714

00:05:47.840 --> 00:05:49.472 Some people would say this is an ill

NOTE Confidence: 0.879687514285714

00:05:49.472 --> 00:05:50.909 posed problem because it's impossible.

NOTE Confidence: 0.879687514285714

00:05:50.910 --> 00:05:52.440 There's just too many mappings.

NOTE Confidence: 0.879687514285714

00:05:52.440 --> 00:05:53.313 But you know,

NOTE Confidence: 0.879687514285714

00:05:53.313 --> 00:05:55.059 I'll leave that for debate later.

NOTE Confidence: 0.879687514285714

00:05:55.060 --> 00:05:55.927 And then finally,

NOTE Confidence: 0.879687514285714

00:05:55.927 --> 00:05:58.555 how do we link this to Spectra of

NOTE Confidence: 0.879687514285714

00:05:58.555 --> 00:05:59.919 behavioral disturbances, right.

NOTE Confidence: 0.879687514285714

00:05:59.919 --> 00:06:02.151 And so I'd like to argue that this

NOTE Confidence: 0.879687514285714

00:06:02.151 --> 00:06:03.909 mapping is fundamentally unknown.

NOTE Confidence: 0.879687514285714

00:06:03.910 --> 00:06:04.794 We don't know it,

NOTE Confidence: 0.879687514285714

00:06:04.794 --> 00:06:06.310 and if somebody argues that we do,

NOTE Confidence: 0.879687514285714

00:06:06.310 --> 00:06:08.980 I think that they're flying.

NOTE Confidence: 0.879687514285714

00:06:08.980 --> 00:06:11.032 Even in circuits where we understand

NOTE Confidence: 0.879687514285714

00:06:11.032 --> 00:06:13.090 our biology very well, like fear,

NOTE Confidence: 0.879687514285714

00:06:13.090 --> 00:06:15.215 we still can't treat PTSD, right?

NOTE Confidence: 0.879687514285714

00:06:15.215 --> 00:06:17.980 So just this mapping is not accomplished,

NOTE Confidence: 0.879687514285714

00:06:17.980 --> 00:06:19.280 right?

NOTE Confidence: 0.879687514285714

00:06:19.280 --> 00:06:21.074 And I actually think that system

NOTE Confidence: 0.879687514285714

00:06:21.074 --> 00:06:22.270 level observations at the

NOTE Confidence: 0.857824136521739

00:06:22.326 --> 00:06:24.132 level of neural systems is where the

NOTE Confidence: 0.857824136521739

00:06:24.132 --> 00:06:25.940 right link to behavior should be,

NOTE Confidence: 0.857824136521739

00:06:25.940 --> 00:06:27.879 not at the level of a synapse,

NOTE Confidence: 0.857824136521739

00:06:27.880 --> 00:06:30.320 because the heterogeneity just explodes,

NOTE Confidence: 0.857824136521739

00:06:30.320 --> 00:06:32.455 the combinatorics become impossible to

NOTE Confidence: 0.857824136521739

00:06:32.455 --> 00:06:34.960 intractable to quantify or deal with.

NOTE Confidence: 0.857824136521739

00:06:34.960 --> 00:06:38.776 So why have we not solved this problem right?

00:06:38.780 --> 00:06:41.258 Why is this opportunity not been realized?

00:06:41.260 --> 00:06:43.780 And so I think that.

00:06:43.780 --> 00:06:46.408 I might argue my many reasons,

00:06:46.410 --> 00:06:47.780 but there's some legacy barriers,

00:06:47.780 --> 00:06:48.796 right, that we're still

00:06:48.796 --> 00:06:50.320 trying to overcome as a field.

00:06:50.320 --> 00:06:54.080 And I and the legacy approach are called

00:06:54.080 --> 00:06:56.848 legacy because it's historically important

00:06:56.848 --> 00:07:00.322 to acknowledge that this this is.

00:07:00.330 --> 00:07:02.004 The framework that we have been

00:07:02.004 --> 00:07:03.455 operating under is has tremendous

00:07:03.455 --> 00:07:05.129 utility for what it was designed

00:07:05.129 --> 00:07:07.226 for and by that I mean DSM, right?

00:07:07.226 --> 00:07:10.610 It does what it was built for to do,

00:07:10.610 --> 00:07:14.173 which is it reliably gets me and

NOTE Confidence: 0.857824136521739

00:07:14.173 --> 00:07:17.675 everybody else to agree that some person

NOTE Confidence: 0.857824136521739

00:07:17.675 --> 00:07:21.809 has X out of P symptoms over T time.

NOTE Confidence: 0.857824136521739

00:07:21.810 --> 00:07:24.090 That it does quantitatively accomplishes

NOTE Confidence: 0.857824136521739

00:07:24.090 --> 00:07:26.640 that, so we can reliably agree.

NOTE Confidence: 0.857824136521739

00:07:26.640 --> 00:07:29.340 To categorize a human being as

NOTE Confidence: 0.857824136521739

00:07:29.340 --> 00:07:31.839 you showed X symptoms out of,

NOTE Confidence: 0.857824136521739

00:07:31.840 --> 00:07:34.500 you know, some rubric overtime.

NOTE Confidence: 0.857824136521739

00:07:34.500 --> 00:07:36.285 And then we give you a label.

NOTE Confidence: 0.857824136521739

00:07:36.290 --> 00:07:37.898 I'd like to argue that's ill

NOTE Confidence: 0.857824136521739

00:07:37.898 --> 00:07:39.310 fitting for what we need,

NOTE Confidence: 0.857824136521739

00:07:39.310 --> 00:07:41.914 actually not wrong for what it was

NOTE Confidence: 0.857824136521739

00:07:41.914 --> 00:07:44.640 built to do, just not what we need.

NOTE Confidence: 0.857824136521739

00:07:44.640 --> 00:07:45.561 And then further,

NOTE Confidence: 0.857824136521739

00:07:45.561 --> 00:07:47.403 we lack data and methods to

NOTE Confidence: 0.857824136521739

00:07:47.403 --> 00:07:48.772 quantitatively molecular benchmark

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13

00:07:48.772 --> 00:07:50.550 brain behavior relationships, right?

00:07:50.550 --> 00:07:52.440 So the legacy approach doesn't have it.

00:07:52.440 --> 00:07:54.378 And then we don't have technological

00:07:54.378 --> 00:07:56.301 solutions to actually scale this with

00:07:56.301 --> 00:07:58.317 the kinds of observations that are so

00:07:58.317 --> 00:08:00.421 important in the area of psychedelic

00:08:00.421 --> 00:08:01.833 medicine for precision therapeutics,

00:08:01.840 --> 00:08:02.348 right.

00:08:02.348 --> 00:08:06.920 So this is a dystopian vision of the future,

00:08:06.920 --> 00:08:07.271 right,

00:08:07.271 --> 00:08:09.728 that I'd like to show sometimes like

00:08:09.728 --> 00:08:12.165 basically where we use computer assisted

00:08:12.165 --> 00:08:14.667 decision making or machine learning informed.

00:08:14.670 --> 00:08:16.240 Decisions with multimodal data where

00:08:16.240 --> 00:08:18.481 the brain is in the middle, right?

00:08:18.481 --> 00:08:20.249 I'm not taking the person out of this.

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00:08:20.250 --> 00:08:21.402 I'm not, you know,

NOTE Confidence: 0.857824136521739

00:08:21.402 --> 00:08:22.554 reductionist to that point,

NOTE Confidence: 0.857824136521739

00:08:22.560 --> 00:08:24.877 but the organ has to be in

NOTE Confidence: 0.857824136521739

00:08:24.877 --> 00:08:26.619 the middle in my mind.

NOTE Confidence: 0.857824136521739

00:08:26.620 --> 00:08:29.080 And then we're hopefully optimizing these

NOTE Confidence: 0.857824136521739

00:08:29.080 --> 00:08:31.779 two decisions through an iterative cycle,

NOTE Confidence: 0.857824136521739

00:08:31.780 --> 00:08:32.110 right?

NOTE Confidence: 0.857824136521739

00:08:32.110 --> 00:08:34.420 But we're not there and and so,

NOTE Confidence: 0.857824136521739

00:08:34.420 --> 00:08:36.254 So what do we do about that?

NOTE Confidence: 0.857824136521739

00:08:36.260 --> 00:08:39.588 So my group here and our other collaborators

NOTE Confidence: 0.857824136521739

00:08:39.588 --> 00:08:43.380 here at Yale are really approaching this in,

NOTE Confidence: 0.857824136521739

00:08:43.380 --> 00:08:44.748 in the following way.

NOTE Confidence: 0.857824136521739

00:08:44.748 --> 00:08:47.880 So let me walk you through the framework.

NOTE Confidence: 0.857824136521739

00:08:47.880 --> 00:08:51.864 So we have to 1st agree that the

NOTE Confidence: 0.857824136521739

00:08:51.864 --> 00:08:53.911 neurobehavioral mapping problem is

NOTE Confidence: 0.857824136521739

00:08:53.911 --> 00:08:56.559 quantitatively A must, we have to do that.

NOTE Confidence: 0.857824136521739

00:08:56.560 --> 00:08:56.827 Correctly.

NOTE Confidence: 0.857824136521739

00:08:56.827 --> 00:08:59.290 And I'll explain what I mean by that, right?

NOTE Confidence: 0.857824136521739

00:08:59.290 --> 00:09:01.530 Because if if we are using an

NOTE Confidence: 0.857824136521739

00:09:01.530 --> 00:09:03.845 ill fitting framework to map

NOTE Confidence: 0.857824136521739

00:09:03.845 --> 00:09:05.447 onto neurobehavioral variation,

NOTE Confidence: 0.857824136521739

00:09:05.450 --> 00:09:07.102 then just won't work.

NOTE Confidence: 0.857824136521739

00:09:07.102 --> 00:09:10.050 We won't even translate what we want.

NOTE Confidence: 0.857824136521739

00:09:10.050 --> 00:09:11.994 Gene expression alterations right

NOTE Confidence: 0.857824136521739

00:09:11.994 --> 00:09:14.424 and disturbances in the way

NOTE Confidence: 0.857824136521739

00:09:14.424 --> 00:09:17.172 that the circuits are formed are

NOTE Confidence: 0.857824136521739

00:09:17.172 --> 00:09:18.618 it's useful information.

NOTE Confidence: 0.857824136521739

00:09:18.618 --> 00:09:21.546 We harness that from say the island

NOTE Confidence: 0.857824136521739

00:09:21.546 --> 00:09:23.870 human brain Atlas to inform our our

NOTE Confidence: 0.857824136521739

00:09:23.937 --> 00:09:26.643 our models that then can simulate

NOTE Confidence: 0.857824136521739

00:09:26.643 --> 00:09:28.890 pharmacological fMRI effects which in

NOTE Confidence: 0.857824136521739

00:09:28.890 --> 00:09:31.110 turn can be fixed individual people.

NOTE Confidence: 0.857824136521739

00:09:31.110 --> 00:09:33.168 So this is just one way

NOTE Confidence: 0.857824136521739

00:09:33.168 --> 00:09:34.540 that we're approaching this

NOTE Confidence: 0.82290617

00:09:34.617 --> 00:09:36.927 problem in the area of just mental

NOTE Confidence: 0.82290617

00:09:36.927 --> 00:09:39.143 health and and psychedelic pharmacology.

NOTE Confidence: 0.82290617

00:09:39.143 --> 00:09:41.208 Specifically, but there's there's many

NOTE Confidence: 0.82290617

00:09:41.208 --> 00:09:44.078 other tools that we're leaving on the table,

NOTE Confidence: 0.82290617

00:09:44.080 --> 00:09:45.502 but this is what I'm going to talk about,

NOTE Confidence: 0.82290617

00:09:45.510 --> 00:09:47.365 right. So again I'd like to argue

NOTE Confidence: 0.82290617

00:09:47.365 --> 00:09:50.029 that you know Chris asked me to talk

NOTE Confidence: 0.82290617

00:09:50.029 --> 00:09:51.473 about neuroimaging today specifically

NOTE Confidence: 0.82290617

00:09:51.473 --> 00:09:53.370 and to really have that focus.

NOTE Confidence: 0.82290617

00:09:53.370 --> 00:09:56.066 So I'd like to argue that new imaging

NOTE Confidence: 0.82290617

00:09:56.066 --> 00:09:59.130 is not an option anymore in our work.

NOTE Confidence: 0.82290617

00:09:59.130 --> 00:10:01.146 And by that I mean normalizing broadly,

NOTE Confidence: 0.82290617

17

00:10:01.150 --> 00:10:03.958 right? But a necessity, because here,

NOTE Confidence: 0.82290617

00:10:03.960 --> 00:10:05.368 here's a choice, right?

NOTE Confidence: 0.82290617

00:10:05.368 --> 00:10:08.408 This is literally what we had on the table,

NOTE Confidence: 0.82290617

00:10:08.410 --> 00:10:11.560 right? But we need this.

NOTE Confidence: 0.82290617

00:10:11.560 --> 00:10:14.565 And so I'd like to argue that if if you

NOTE Confidence: 0.82290617

00:10:14.565 --> 00:10:16.362 present the problem this way, right,

NOTE Confidence: 0.82290617

00:10:16.362 --> 00:10:18.938 like how can we not leverage brain data

NOTE Confidence: 0.82290617

00:10:18.938 --> 00:10:22.014 in the service of decision making as a must,

NOTE Confidence: 0.82290617

00:10:22.020 --> 00:10:24.190 specifically for things as complicated

NOTE Confidence: 0.82290617

00:10:24.190 --> 00:10:25.926 as psychedelic neurobiology at

NOTE Confidence: 0.82290617

00:10:25.926 --> 00:10:27.773 the individual level, right.

NOTE Confidence: 0.82290617

00:10:27.773 --> 00:10:28.116 So.

NOTE Confidence: 0.82290617

00:10:28.116 --> 00:10:30.860 So, OK, so how can we exploit imaging

NOTE Confidence: 0.82290617

00:10:30.936 --> 00:10:32.940 in the service of this goal?

NOTE Confidence: 0.82290617

00:10:32.940 --> 00:10:34.760 So that's the rest of the talk.

NOTE Confidence: 0.82290617

00:10:34.760 --> 00:10:38.484 So for those of you who haven't

18

NOTE Confidence: 0.82290617

00:10:38.484 --> 00:10:40.080 really thought about.

NOTE Confidence: 0.82290617

00:10:40.080 --> 00:10:41.220 Structural functional

NOTE Confidence: 0.82290617

00:10:41.220 --> 00:10:42.930 multimodal imaging recently,

NOTE Confidence: 0.82290617

00:10:42.930 --> 00:10:44.882 this is a very useful reminder of the

NOTE Confidence: 0.82290617

00:10:44.882 --> 00:10:46.530 resolution of what imaging straddles,

NOTE Confidence: 0.82290617

00:10:46.530 --> 00:10:46.906 right.

NOTE Confidence: 0.82290617

00:10:46.906 --> 00:10:50.290 So on the Y axis is the size of

NOTE Confidence: 0.82290617

00:10:50.395 --> 00:10:53.510 the observation and time is on the

NOTE Confidence: 0.82290617

00:10:53.510 --> 00:10:56.300 the X axis and and you'll notice

NOTE Confidence: 0.82290617

00:10:56.300 --> 00:10:58.050 that human imaging across modality

NOTE Confidence: 0.82290617

00:10:58.050 --> 00:11:00.006 straddles a good bit of the space.

NOTE Confidence: 0.82290617

00:11:00.010 --> 00:11:01.478 We're not helpless right.

NOTE Confidence: 0.82290617

00:11:01.478 --> 00:11:03.680 Like we can actually measure signals

NOTE Confidence: 0.82290617

00:11:03.745 --> 00:11:06.286 in various ways in relation to various

NOTE Confidence: 0.82290617

00:11:06.286 --> 00:11:07.790 phenomena, but we still are, you know,

NOTE Confidence: 0.82290617

00:11:07.790 --> 00:11:10.446 out of reach of certain levels of analysis.

NOTE Confidence: 0.82290617

00:11:10.450 --> 00:11:12.154 Like with human imaging with symptoms

NOTE Confidence: 0.82290617

00:11:12.154 --> 00:11:13.899 improving but still not quite there.

NOTE Confidence: 0.82290617

00:11:13.900 --> 00:11:15.594 And we also don't have just one

NOTE Confidence: 0.82290617

00:11:15.594 --> 00:11:16.640 way to measure this,

NOTE Confidence: 0.82290617

00:11:16.640 --> 00:11:17.092 right.

NOTE Confidence: 0.82290617

00:11:17.092 --> 00:11:20.256 We have multiple modalities that now can

NOTE Confidence: 0.82290617

00:11:20.256 --> 00:11:23.045 combine that give you different slices

NOTE Confidence: 0.82290617

00:11:23.045 --> 00:11:25.757 of the signal that this incredibly

NOTE Confidence: 0.82290617

00:11:25.833 --> 00:11:28.318 complex piece of tissue produces,

NOTE Confidence: 0.82290617

00:11:28.320 --> 00:11:28.642 right.

NOTE Confidence: 0.82290617

00:11:28.642 --> 00:11:29.286 And so,

NOTE Confidence: 0.82290617

00:11:29.286 --> 00:11:31.540 so I'm going to talk about specifically

NOTE Confidence: 0.82290617

00:11:31.609 --> 00:11:34.300 throughout the rest of talk about bold F MRI,

NOTE Confidence: 0.82290617

00:11:34.300 --> 00:11:38.900 right, which is a measure that is is.

NOTE Confidence: 0.82290617

00:11:38.900 --> 00:11:41.060 One of the expertise areas in my group,

NOTE Confidence: 0.82290617

00:11:41.060 --> 00:11:43.700 right so.

NOTE Confidence: 0.82290617

00:11:43.700 --> 00:11:44.095 Specifically,

NOTE Confidence: 0.82290617

00:11:44.095 --> 00:11:46.465 the phenomena that for the rest

NOTE Confidence: 0.82290617

00:11:46.465 --> 00:11:49.447 of the the talk will focus on is

NOTE Confidence: 0.82290617

00:11:49.447 --> 00:11:51.420 this idea of resting state, right?

NOTE Confidence: 0.82290617

00:11:51.420 --> 00:11:53.340 And so this is now a household name.

NOTE Confidence: 0.82290617

00:11:53.340 --> 00:11:53.898 I, you know,

NOTE Confidence: 0.82290617

00:11:53.898 --> 00:11:55.200 I don't have to go over this

NOTE Confidence: 0.82290617

00:11:55.254 --> 00:11:56.119 in a lot of detail,

NOTE Confidence: 0.82290617

00:11:56.120 --> 00:11:57.723 but I'd like to kind of just

NOTE Confidence: 0.82290617

00:11:57.723 --> 00:11:58.759 review the history of it.

NOTE Confidence: 0.82290617

00:11:58.760 --> 00:12:00.672 I always like to do this because I

NOTE Confidence: 0.82290617

00:12:00.672 --> 00:12:03.093 like to remind people that in 1995,

NOTE Confidence: 0.82290617

00:12:03.093 --> 00:12:05.142 right, broad Biswal.

NOTE Confidence: 0.82290617

00:12:05.142 --> 00:12:07.874 Actually observe this simply

NOTE Confidence: 0.82290617

00:12:07.874 --> 00:12:10.090 by taking signal.

NOTE Confidence: 0.82290617

00:12:10.090 --> 00:12:12.918 Out of 1 hemisphere of the motor

NOTE Confidence: 0.82290617

00:12:12.918 --> 00:12:15.306 cortex and asking where in the

NOTE Confidence: 0.82290617

00:12:15.306 --> 00:12:17.190 brain is there time dependent

NOTE Confidence: 0.82290617

00:12:17.190 --> 00:12:19.470 covariation of signal within a person

NOTE Confidence: 0.82290617

00:12:19.537 --> 00:12:21.467 and then average across people.

NOTE Confidence: 0.82290617

00:12:21.470 --> 00:12:24.278 And he saw this map right which is

NOTE Confidence: 0.82290617

00:12:24.278 --> 00:12:26.249 bilateral motor cortex comes out.

NOTE Confidence: 0.82290617

00:12:26.250 --> 00:12:28.326 And people thought this was junk.

NOTE Confidence: 0.82290617

00:12:28.330 --> 00:12:29.810 This was a compound, right?

NOTE Confidence: 0.82290617

00:12:29.810 --> 00:12:31.194 And they ignored it.

NOTE Confidence: 0.82290617

00:12:31.194 --> 00:12:33.330 In fact, he was attacked for it quite a lot,

NOTE Confidence: 0.883748563333333

00:12:33.330 --> 00:12:35.610 right? And then only a

NOTE Confidence: 0.883748563333333

00:12:35.610 --> 00:12:37.434 decade later with some.

NOTE Confidence: 0.544249814625

00:12:39.540 --> 00:12:41.060 Advances from Michael Greicius

NOTE Confidence: 0.544249814625

00:12:41.060 --> 00:12:42.580 and then Marcus Raichle.

00:12:42.580 --> 00:12:44.500 Did this phenomena really

00:12:44.500 --> 00:12:45.940 become a mainstream?

00:12:45.940 --> 00:12:47.613 And so now if you Fast forward

00:12:47.613 --> 00:12:49.130 what is now a decade ago,

00:12:49.130 --> 00:12:50.378 which is hard to believe right,

00:12:50.380 --> 00:12:53.896 that Thomas Yao and Randy Buckner

00:12:53.896 --> 00:12:56.240 actually mapped comprehensively right.

00:12:56.240 --> 00:12:57.779 Large scale networks

00:12:57.779 --> 00:12:59.318 across individuals right.

00:12:59.320 --> 00:13:02.500 And this is this is now a joke

00:13:02.500 --> 00:13:04.173 like we we know we can do this now

00:13:04.173 --> 00:13:05.478 and every single person right.

00:13:05.480 --> 00:13:06.944 But it was controversial

00:13:06.944 --> 00:13:09.140 then and so then 2016 onward.

00:13:09.140 --> 00:13:10.832 Human connectome produced sparse

00:13:10.832 --> 00:13:13.830 relation which gives you an index of

NOTE Confidence: 0.544249814625

00:13:13.830 --> 00:13:16.176 the boundaries between the areas that

NOTE Confidence: 0.544249814625

00:13:16.176 --> 00:13:18.379 is comprehensive but not definitive.

NOTE Confidence: 0.544249814625

00:13:18.380 --> 00:13:20.424 This will probably improve it or actively,

NOTE Confidence: 0.544249814625

00:13:20.430 --> 00:13:21.846 but I'd like to tell you like we've

NOTE Confidence: 0.544249814625

00:13:21.846 --> 00:13:23.218 made some serious progress, right,

NOTE Confidence: 0.544249814625

00:13:23.218 --> 00:13:25.990 with human or imaging and we can exploit it,

NOTE Confidence: 0.544249814625

00:13:25.990 --> 00:13:26.578 right?

NOTE Confidence: 0.544249814625

00:13:26.578 --> 00:13:27.754 And furthermore,

NOTE Confidence: 0.544249814625

00:13:27.754 --> 00:13:31.282 this is something I will repeat

NOTE Confidence: 0.544249814625

00:13:31.282 --> 00:13:33.798 in every talk I give.

NOTE Confidence: 0.544249814625

00:13:33.800 --> 00:13:36.068 So the reason why the Human

NOTE Confidence: 0.544249814625

00:13:36.068 --> 00:13:37.964 Connectome project pipelines and the

NOTE Confidence: 0.544249814625

00:13:37.964 --> 00:13:39.688 entire effort towards so impactful,

NOTE Confidence: 0.544249814625

00:13:39.688 --> 00:13:42.236 which is why I obviously drink the

NOTE Confidence: 0.544249814625

00:13:42.236 --> 00:13:46.410 kool-aid because I trained there, but.

NOTE Confidence: 0.544249814625

00:13:46.410 --> 00:13:48.912 The human brain and the cortical

NOTE Confidence: 0.544249814625

00:13:48.912 --> 00:13:51.117 mantle is A2 dimensional surface

NOTE Confidence: 0.544249814625

00:13:51.117 --> 00:13:53.883 wrapped around white matter that is

NOTE Confidence: 0.544249814625

00:13:53.883 --> 00:13:56.598 about 4 millimeters thick and it's the

NOTE Confidence: 0.544249814625

00:13:56.598 --> 00:13:59.254 size of a pizza and that geometry matters.

NOTE Confidence: 0.544249814625

00:13:59.254 --> 00:14:01.164 It matters fundamentally when you're

NOTE Confidence: 0.544249814625

00:14:01.164 --> 00:14:03.316 going to do precision medicine

NOTE Confidence: 0.544249814625

00:14:03.316 --> 00:14:05.196 analytics with single subject

NOTE Confidence: 0.544249814625

00:14:05.196 --> 00:14:06.824 human cortical surfaces, right?

NOTE Confidence: 0.544249814625

00:14:06.824 --> 00:14:07.252 In fact,

NOTE Confidence: 0.544249814625

00:14:07.252 --> 00:14:08.750 just before this talk I got off

NOTE Confidence: 0.544249814625

00:14:08.803 --> 00:14:10.308 the call with one of my students,

NOTE Confidence: 0.544249814625

00:14:10.310 --> 00:14:11.050 Amber Howell,

NOTE Confidence: 0.544249814625

00:14:11.050 --> 00:14:12.900 deeply debating the importance of

NOTE Confidence: 0.544249814625

00:14:12.900 --> 00:14:14.383 importance of social curvature

NOTE Confidence: 0.544249814625

00:14:14.383 --> 00:14:16.243 and depth on a single subject

NOTE Confidence: 0.544249814625

00:14:16.243 --> 00:14:17.400 level in relation to.

NOTE Confidence: 0.544249814625

00:14:17.400 --> 00:14:19.170 Diffusivity of white matter tracts,

NOTE Confidence: 0.544249814625

00:14:19.170 --> 00:14:20.420 and turns out it matters.

NOTE Confidence: 0.544249814625

00:14:20.420 --> 00:14:22.990 It matters a lot anyway.

NOTE Confidence: 0.544249814625

00:14:22.990 --> 00:14:25.168 Analyzing your data on the surface,

NOTE Confidence: 0.544249814625

00:14:25.170 --> 00:14:28.878 I think is is. I must like you.

NOTE Confidence: 0.544249814625

00:14:28.878 --> 00:14:30.630 You are blind without that to

NOTE Confidence: 0.544249814625

00:14:30.696 --> 00:14:33.240 individual variation, right?

NOTE Confidence: 0.544249814625

00:14:33.240 --> 00:14:34.450 So.

NOTE Confidence: 0.544249814625

00:14:34.450 --> 00:14:35.930 When you do this right,

NOTE Confidence: 0.544249814625

00:14:35.930 --> 00:14:39.142 then you can produce metrics in the

NOTE Confidence: 0.544249814625

00:14:39.142 --> 00:14:41.272 geometry of the cortical surface

NOTE Confidence: 0.544249814625

00:14:41.272 --> 00:14:43.886 that can quantify some signal in

NOTE Confidence: 0.544249814625

00:14:43.886 --> 00:14:45.986 every cortical parcel or area.

NOTE Confidence: 0.544249814625

00:14:45.990 --> 00:14:48.042 I'll use the term parcel because

NOTE Confidence: 0.544249814625

00:14:48.042 --> 00:14:49.410 that's the formal definition.

NOTE Confidence: 0.544249814625

00:14:49.410 --> 00:14:51.328 And then you can operate with those

NOTE Confidence: 0.544249814625

00:14:51.328 --> 00:14:53.053 metrics to analyze it within a

NOTE Confidence: 0.544249814625

00:14:53.053 --> 00:14:54.745 subject across people in various ways,

NOTE Confidence: 0.544249814625

00:14:54.750 --> 00:14:55.118 right.

NOTE Confidence: 0.544249814625

00:14:55.118 --> 00:14:55.854 So furthermore,

NOTE Confidence: 0.544249814625

00:14:55.854 --> 00:14:59.389 what we've done in my group out of necessity,

NOTE Confidence: 0.544249814625

00:14:59.390 --> 00:14:59.723 right,

NOTE Confidence: 0.544249814625

00:14:59.723 --> 00:15:02.054 we started to use the cortical parcellation

NOTE Confidence: 0.544249814625

00:15:02.054 --> 00:15:04.188 from the Human Connectome Project,

NOTE Confidence: 0.544249814625

00:15:04.190 --> 00:15:05.566 which is shown here.

NOTE Confidence: 0.544249814625

00:15:05.566 --> 00:15:06.598 These little borders,

NOTE Confidence: 0.544249814625

00:15:06.600 --> 00:15:09.200 but then we use the network partitions from

NOTE Confidence: 0.544249814625

00:15:09.200 --> 00:15:11.538 from other groups and they were great,

NOTE Confidence: 0.544249814625

00:15:11.540 --> 00:15:12.840 they they worked really well.

NOTE Confidence: 0.544249814625

00:15:12.840 --> 00:15:15.220 But then we realized subcortical

NOTE Confidence: 0.544249814625

00:15:15.220 --> 00:15:17.124 coverage is not there.

NOTE Confidence: 0.544249814625

00:15:17.130 --> 00:15:18.920 Like thalamus wasn't covered appropriately,

NOTE Confidence: 0.544249814625

00:15:18.920 --> 00:15:20.366 brainstem wasn't covered.

NOTE Confidence: 0.544249814625

00:15:20.366 --> 00:15:23.268 And you guys know that psychiatric

NOTE Confidence: 0.544249814625

00:15:23.268 --> 00:15:25.220 medication works on subcortical

NOTE Confidence: 0.544249814625

00:15:25.220 --> 00:15:27.660 circuits and precision of isolating

NOTE Confidence: 0.544249814625

00:15:27.727 --> 00:15:29.612 specific voxels in relation to

NOTE Confidence: 0.544249814625

00:15:29.612 --> 00:15:32.180 networks and parcels is really important.

NOTE Confidence: 0.544249814625

00:15:32.180 --> 00:15:34.112 So what I'm showing you here is

NOTE Confidence: 0.544249814625

00:15:34.112 --> 00:15:35.920 work produced by my student Lisa.

NOTE Confidence: 0.544249814625

00:15:35.920 --> 00:15:38.655 Who's extended the cortical partition

NOTE Confidence: 0.544249814625

00:15:38.655 --> 00:15:40.843 into networks Cortically first,

NOTE Confidence: 0.544249814625

00:15:40.850 --> 00:15:43.855 and then studied how subcortical

NOTE Confidence: 0.544249814625

00:15:43.855 --> 00:15:46.860 voxels covary with those networks,

NOTE Confidence: 0.544249814625

00:15:46.860 --> 00:15:49.260 assigning every single voxel in

28

NOTE Confidence: 0.544249814625

00:15:49.260 --> 00:15:51.660 subcortical brain matter to a

NOTE Confidence: 0.544249814625

00:15:51.744 --> 00:15:54.576 network until it reached split half?

NOTE Confidence: 0.814083745

00:15:54.580 --> 00:15:57.598 Stability across the entire HCP sample.

NOTE Confidence: 0.814083745

00:15:57.600 --> 00:15:58.937 And so the reason why we did

NOTE Confidence: 0.814083745

00:15:58.937 --> 00:16:00.777 this out of necessity is we need

NOTE Confidence: 0.814083745

00:16:00.777 --> 00:16:01.993 this for clinical application.

NOTE Confidence: 0.814083745

00:16:02.000 --> 00:16:04.044 We actually needed a whole brain partition

NOTE Confidence: 0.814083745

00:16:04.044 --> 00:16:06.040 to covers every piece of Gray matter.

NOTE Confidence: 0.814083745

00:16:06.040 --> 00:16:07.979 We can't leave things on the table.

NOTE Confidence: 0.814083745

00:16:07.980 --> 00:16:09.771 So now this is published and this is what

NOTE Confidence: 0.814083745

00:16:09.771 --> 00:16:11.419 we're going to be using for us to talk.

NOTE Confidence: 0.814083745

00:16:11.420 --> 00:16:13.352 Now just to convince you that

NOTE Confidence: 0.814083745

00:16:13.352 --> 00:16:14.977 this actually is better, right.

NOTE Confidence: 0.814083745

00:16:14.977 --> 00:16:17.575 So you can take a dense signal, right?

NOTE Confidence: 0.814083745

00:16:17.575 --> 00:16:19.455 In other words, at the level of vertex

NOTE Confidence: 0.814083745

00:16:19.455 --> 00:16:21.586 on a cortical surface, you can parse,

NOTE Confidence: 0.814083745

00:16:21.586 --> 00:16:23.398 relate it prior to computing some

NOTE Confidence: 0.814083745

00:16:23.398 --> 00:16:25.239 metric or you can parse relate it.

NOTE Confidence: 0.814083745

00:16:25.240 --> 00:16:26.274 Post right?

NOTE Confidence: 0.814083745

00:16:26.274 --> 00:16:29.376 So if the person relation is.

NOTE Confidence: 0.814083745

00:16:29.380 --> 00:16:31.820 Valid and consistent across subjects,

NOTE Confidence: 0.814083745

00:16:31.820 --> 00:16:34.074 then this should be better than that.

NOTE Confidence: 0.814083745

00:16:34.080 --> 00:16:35.348 And that's in fact true, right?

NOTE Confidence: 0.814083745

00:16:35.348 --> 00:16:36.776 And so this is not news,

NOTE Confidence: 0.814083745

00:16:36.780 --> 00:16:37.880 not Glasser has shown this

NOTE Confidence: 0.814083745

00:16:37.880 --> 00:16:39.180 in his work and so on,

NOTE Confidence: 0.814083745

00:16:39.180 --> 00:16:41.988 but it's just to convince you guys that

NOTE Confidence: 0.814083745

00:16:41.988 --> 00:16:43.840 these parcellation are actually very,

NOTE Confidence: 0.814083745

00:16:43.840 --> 00:16:46.220 very useful, not just quantitatively,

NOTE Confidence: 0.814083745

00:16:46.220 --> 00:16:48.536 but as a feature space reduction,

NOTE Confidence: 0.814083745

00:16:48.540 --> 00:16:50.448 because now you are no longer

NOTE Confidence: 0.814083745

00:16:50.448 --> 00:16:51.698 working with 95,000 voxels,

NOTE Confidence: 0.814083745

00:16:51.698 --> 00:16:53.218 you're working with 700 areas

NOTE Confidence: 0.814083745

00:16:53.218 --> 00:16:55.358 and now you can do some clever

NOTE Confidence: 0.814083745

00:16:55.358 --> 00:16:57.116 feature engineering on top of that.

NOTE Confidence: 0.814083745

00:16:57.120 --> 00:16:58.540 So that matters, right?

NOTE Confidence: 0.814083745

00:16:58.540 --> 00:17:01.862 So how do we now link this to

NOTE Confidence: 0.814083745

00:17:01.862 --> 00:17:03.603 molecular mechanism, right,

NOTE Confidence: 0.814083745

00:17:03.603 --> 00:17:06.768 very broadly speaking and so.

NOTE Confidence: 0.814083745

00:17:06.770 --> 00:17:07.244 So, so,

NOTE Confidence: 0.814083745

00:17:07.244 --> 00:17:09.140 so the way we do this and the

NOTE Confidence: 0.814083745

00:17:09.204 --> 00:17:11.124 way we've approached this across

NOTE Confidence: 0.814083745

00:17:11.124 --> 00:17:12.982 all compounds ketamine,

NOTE Confidence: 0.814083745

00:17:12.982 --> 00:17:17.398 single sideband as well as application

NOTE Confidence: 0.814083745

00:17:17.398 --> 00:17:20.673 to clinical questions is what

NOTE Confidence: 0.814083745

00:17:20.673 --> 00:17:23.077 are the principal organizational.

NOTE Confidence: 0.875419238571428

00:17:26.120 --> 00:17:28.010 Features, if you will, of the human

NOTE Confidence: 0.875419238571428

00:17:28.010 --> 00:17:30.399 brain or the mammalian brain in general,

NOTE Confidence: 0.875419238571428

00:17:30.400 --> 00:17:32.520 and I'd like to argue one that we know about,

NOTE Confidence: 0.875419238571428

00:17:32.520 --> 00:17:34.266 is functional specialization

NOTE Confidence: 0.875419238571428

00:17:34.266 --> 00:17:36.594 across the cortical axis.

NOTE Confidence: 0.875419238571428

00:17:36.600 --> 00:17:38.864 So we know that lower order and higher

NOTE Confidence: 0.875419238571428

00:17:38.864 --> 00:17:41.333 order areas have very distinct patterns of

NOTE Confidence: 0.875419238571428

00:17:41.333 --> 00:17:43.500 feed forward and back connections, right?

NOTE Confidence: 0.875419238571428

00:17:43.500 --> 00:17:45.100 So that's an organizational principle.

NOTE Confidence: 0.875419238571428

00:17:45.100 --> 00:17:47.340 This is a classic picture from the

NOTE Confidence: 0.875419238571428

00:17:47.340 --> 00:17:48.961 Fellman and Vanessa and publication,

NOTE Confidence: 0.875419238571428

00:17:48.961 --> 00:17:51.908 which also highlights that there is a

NOTE Confidence: 0.875419238571428

00:17:51.908 --> 00:17:54.669 hierarchy and information processing from.

NOTE Confidence: 0.875419238571428

00:17:54.670 --> 00:17:56.880 Answer to association agents, right?

NOTE Confidence: 0.875419238571428

00:17:56.880 --> 00:18:00.648 We also know from work such as this

NOTE Confidence: 0.875419238571428

00:18:00.648 --> 00:18:04.159 paper from John Murray while he was

NOTE Confidence: 0.875419238571428

00:18:04.160 --> 00:18:06.428 starting here at Yale that there

NOTE Confidence: 0.875419238571428

00:18:06.428 --> 00:18:09.130 is a difference in the spontaneous

NOTE Confidence: 0.875419238571428

00:18:09.130 --> 00:18:11.354 autocorrelated activity across areas

NOTE Confidence: 0.875419238571428

00:18:11.354 --> 00:18:15.103 from non human primate data and this

NOTE Confidence: 0.875419238571428

00:18:15.103 --> 00:18:17.031 intrinsic activity scales suggesting

NOTE Confidence: 0.875419238571428

00:18:17.031 --> 00:18:19.458 a hierarchy of functional hierarchy.

NOTE Confidence: 0.875419238571428

00:18:19.458 --> 00:18:19.947 Furthermore,

NOTE Confidence: 0.875419238571428

00:18:19.947 --> 00:18:22.881 we know that during cognitive operations

NOTE Confidence: 0.875419238571428

00:18:22.881 --> 00:18:24.950 such as working memory primary.

NOTE Confidence: 0.875419238571428

00:18:24.950 --> 00:18:28.710 Visual areas such as Mt do not sustain

NOTE Confidence: 0.875419238571428

00:18:28.710 --> 00:18:31.527 signal during the mnemonic phase,

NOTE Confidence: 0.875419238571428

00:18:31.530 --> 00:18:35.352 whereas areas such as LP FC sustain

NOTE Confidence: 0.875419238571428

00:18:35.352 --> 00:18:37.890 a recurrent reverberatory activity,

NOTE Confidence: 0.875419238571428

00:18:37.890 --> 00:18:39.902 right again highlighting distinct

NOTE Confidence: 0.875419238571428

00:18:39.902 --> 00:18:41.914 functional specialization in this

NOTE Confidence: 0.875419238571428

00:18:41.914 --> 00:18:43.240 very coarse way.

NOTE Confidence: 0.875419238571428

00:18:43.240 --> 00:18:47.244 Furthermore, we know that we can leverage.

NOTE Confidence: 0.875419238571428

00:18:47.250 --> 00:18:51.044 Microstructure values from the T1 and T2

NOTE Confidence: 0.875419238571428

00:18:51.044 --> 00:18:55.626 maps to derive a proxy of myelin cortically,

NOTE Confidence: 0.875419238571428

00:18:55.630 --> 00:18:57.818 which shows a hierarchy.

NOTE Confidence: 0.875419238571428

00:18:57.818 --> 00:19:00.006 It smoothly varies from

NOTE Confidence: 0.875419238571428

00:19:00.006 --> 00:19:02.409 association to sensory areas.

NOTE Confidence: 0.875419238571428

00:19:02.410 --> 00:19:05.050 And this is also true in the macaque,

NOTE Confidence: 0.875419238571428

00:19:05.050 --> 00:19:05.305 right?

NOTE Confidence: 0.875419238571428

00:19:05.305 --> 00:19:07.345 So now we have some clues that the

NOTE Confidence: 0.875419238571428

00:19:07.345 --> 00:19:09.458 brain varies hierarchically and this

NOTE Confidence: 0.875419238571428

00:19:09.458 --> 00:19:11.352 shouldn't be controversial, right?

NOTE Confidence: 0.875419238571428

00:19:11.352 --> 00:19:14.604 Can we leverage this information to

NOTE Confidence: 0.875419238571428

00:19:14.604 --> 00:19:17.502 understand how the effects of pharmacology?

NOTE Confidence: 0.875419238571428

00:19:17.502 --> 00:19:20.220 Which we'll get to and so.

NOTE Confidence: 0.875419238571428

00:19:20.220 --> 00:19:22.642 The the motivation for this work was

NOTE Confidence: 0.875419238571428

00:19:22.642 --> 00:19:25.710 driven by a grad student in John's lab,

NOTE Confidence: 0.875419238571428

00:19:25.710 --> 00:19:28.002 Josh Burt, who did some really

NOTE Confidence: 0.875419238571428

00:19:28.002 --> 00:19:29.530 elegant gene expression mapping.

NOTE Confidence: 0.875419238571428

00:19:29.530 --> 00:19:31.066 And I'll walk you through why this matters,

NOTE Confidence: 0.875419238571428

00:19:31.070 --> 00:19:31.362 right.

NOTE Confidence: 0.875419238571428

00:19:31.362 --> 00:19:33.774 So we have this human myelin map, right?

NOTE Confidence: 0.875419238571428

00:19:33.774 --> 00:19:35.958 We've established that it has a

NOTE Confidence: 0.875419238571428

00:19:35.958 --> 00:19:36.988 hierarchical organization, right.

NOTE Confidence: 0.875419238571428

00:19:36.988 --> 00:19:39.074 And what he's just shown that when

NOTE Confidence: 0.875419238571428

00:19:39.074 --> 00:19:41.189 you use Lisas network partition,

NOTE Confidence: 0.875419238571428

00:19:41.190 --> 00:19:43.367 but in fact there is a difference

NOTE Confidence: 0.875419238571428

00:19:43.367 --> 00:19:43.989 across networks,

NOTE Confidence: 0.875419238571428

00:19:43.990 --> 00:19:44.350 right,

NOTE Confidence: 0.875419238571428

00:19:44.350 --> 00:19:46.510 that the association networks have less

NOTE Confidence: 0.875419238571428

00:19:46.510 --> 00:19:48.789 myelin than sensory somatomotor networks.

NOTE Confidence: 0.875419238571428

00:19:48.790 --> 00:19:50.720 OK, just the validity check.

NOTE Confidence: 0.875419238571428

00:19:50.720 --> 00:19:51.213 Furthermore,

NOTE Confidence: 0.875419238571428

00:19:51.213 --> 00:19:53.678 he's taken mcac myelin values,

NOTE Confidence: 0.875419238571428

00:19:53.680 --> 00:19:56.080 and he's taken tracer data,

NOTE Confidence: 0.875419238571428

00:19:56.080 --> 00:19:57.795 defining the hierarchy as feed

NOTE Confidence: 0.875419238571428

00:19:57.795 --> 00:19:59.510 forward and feedback connections in

NOTE Confidence: 0.875419238571428

00:19:59.566 --> 00:20:01.696 collaboration with David Vanessa's group.

NOTE Confidence: 0.875419238571428

00:20:01.700 --> 00:20:03.035 And he's correlated.

NOTE Confidence: 0.875419238571428

00:20:03.035 --> 00:20:04.815 This again establishing that

NOTE Confidence: 0.875419238571428

00:20:04.815 --> 00:20:06.610 there is hierarchy right.

NOTE Confidence: 0.875419238571428

00:20:06.610 --> 00:20:07.382 So far,

NOTE Confidence: 0.875419238571428

00:20:07.382 --> 00:20:08.154 so good.

NOTE Confidence: 0.875419238571428

00:20:08.154 --> 00:20:11.192 Then he went into the alien human

NOTE Confidence: 0.875419238571428

00:20:11.192 --> 00:20:14.337 Brain Atlas gene expression database.

NOTE Confidence: 0.875419238571428

00:20:14.340 --> 00:20:17.538 And he's taken from every cortical

NOTE Confidence: 0.875419238571428

00:20:17.538 --> 00:20:20.437 microarray a probe across something

36

NOTE Confidence: 0.875419238571428

00:20:20.437 --> 00:20:23.137 like 20,000 different genes.

NOTE Confidence: 0.875419238571428

00:20:23.140 --> 00:20:25.420 And because the amount of human

NOTE Confidence: 0.875419238571428

00:20:25.420 --> 00:20:26.940 brain Atlas has serendipitously,

NOTE Confidence: 0.875419238571428

00:20:26.940 --> 00:20:27.854 thank goodness,

NOTE Confidence: 0.875419238571428

00:20:27.854 --> 00:20:30.139 scanned every single person of

NOTE Confidence: 0.875419238571428

00:20:30.139 --> 00:20:32.940 the six people that they studied.

NOTE Confidence: 0.875419238571428

00:20:32.940 --> 00:20:33.454 Postmortem.

NOTE Confidence: 0.875419238571428

00:20:33.454 --> 00:20:36.538 We could then reconstruct the cortical

NOTE Confidence: 0.875419238571428

00:20:36.538 --> 00:20:39.176 surface right anatomy postmortem and

NOTE Confidence: 0.875419238571428

00:20:39.176 --> 00:20:43.012 map it onto the human Connectome Atlas.

NOTE Confidence: 0.875419238571428

00:20:43.020 --> 00:20:45.015 Particulate it right using the

NOTE Confidence: 0.875419238571428

00:20:45.015 --> 00:20:47.010 parcellation that I just introduced.

NOTE Confidence: 0.875419238571428

00:20:47.010 --> 00:20:49.677 Do this for every person from the

NOTE Confidence: 0.875419238571428

00:20:49.677 --> 00:20:52.039 island human brain Atlas and then

NOTE Confidence: 0.875419238571428

00:20:52.039 --> 00:20:54.325 average it to get the aggregate

NOTE Confidence: 0.875419238571428

00:20:54.325 --> 00:20:56.537 group map across every gene

NOTE Confidence: 0.875419238571428

00:20:56.537 --> 00:20:58.293 for every cortical parcel.

NOTE Confidence: 0.875419238571428

00:20:58.300 --> 00:20:59.996 Now you can imagine why this is powerful.

NOTE Confidence: 0.859097170434783

00:21:00.000 --> 00:21:02.149 Now we have an actual gene expression

NOTE Confidence: 0.859097170434783

00:21:02.149 --> 00:21:03.613 topography for every gene across

NOTE Confidence: 0.859097170434783

00:21:03.613 --> 00:21:05.314 all the areas that we have our

NOTE Confidence: 0.859097170434783

00:21:05.314 --> 00:21:06.800 new imaging maps for, right?

NOTE Confidence: 0.859097170434783

00:21:06.800 --> 00:21:08.760 So what can we do with this?

NOTE Confidence: 0.859097170434783

00:21:08.760 --> 00:21:10.000 So the first question is,

NOTE Confidence: 0.859097170434783

00:21:10.000 --> 00:21:12.080 what is the principal gradient,

NOTE Confidence: 0.859097170434783

00:21:12.080 --> 00:21:14.630 the first principal component of

NOTE Confidence: 0.859097170434783

00:21:14.630 --> 00:21:16.446 gene expression topography, right.

NOTE Confidence: 0.859097170434783

00:21:16.446 --> 00:21:17.876 And this is the picture.

NOTE Confidence: 0.859097170434783

00:21:17.880 --> 00:21:19.453 This is how it varies, right?

NOTE Confidence: 0.859097170434783

00:21:19.453 --> 00:21:21.518 And it varies this way,

NOTE Confidence: 0.859097170434783

00:21:21.520 --> 00:21:22.650 so much so that it

NOTE Confidence: 0.783418904545454

00:21:23.290 --> 00:21:25.663 did you say that this this expression

NOTE Confidence: 0.783418904545454

00:21:25.663 --> 00:21:28.910 is from 6 brains, six people. OK.

NOTE Confidence: 0.783418904545454

00:21:28.910 --> 00:21:30.910 So I'm wondering how that limits the power

NOTE Confidence: 0.783418904545454

00:21:30.910 --> 00:21:32.949 of this kind of correlation analysis.

NOTE Confidence: 0.783418904545454

00:21:32.950 --> 00:21:34.777 If you only have you have a huge number

NOTE Confidence: 0.783418904545454

00:21:34.777 --> 00:21:37.580 of genes but you only have 6 replicates

NOTE Confidence: 0.783418904545454

00:21:37.580 --> 00:21:40.188 at each for each gene in each parcel,

NOTE Confidence: 0.829708503333333

00:21:40.500 --> 00:21:41.404 that's a great question.

NOTE Confidence: 0.829708503333333

00:21:41.404 --> 00:21:42.534 So let me go back.

NOTE Confidence: 0.829708503333333

00:21:42.540 --> 00:21:45.372 So, So what Chris is really

NOTE Confidence: 0.829708503333333

00:21:45.372 --> 00:21:47.590 highlighting is something that is.

NOTE Confidence: 0.829708503333333

00:21:47.590 --> 00:21:51.550 Rental, which is you when you're running any

NOTE Confidence: 0.829708503333333

00:21:51.550 --> 00:21:55.378 analysis on the matrix of genes by parcels,

NOTE Confidence: 0.829708503333333

00:21:55.380 --> 00:21:57.866 notice that their group averaged, right?

NOTE Confidence: 0.829708503333333

00:21:57.866 --> 00:22:01.918 So what we do is we first ask, what is the?

NOTE Confidence: 0.829708503333333

00:22:01.918 --> 00:22:04.048 Coverage of that microarray probe

NOTE Confidence: 0.829708503333333

00:22:04.048 --> 00:22:06.630 in that cortical location, right.

NOTE Confidence: 0.829708503333333

00:22:06.630 --> 00:22:07.730 Is there a good signal?

NOTE Confidence: 0.829708503333333

00:22:07.730 --> 00:22:10.250 And then we evaluate the differential

NOTE Confidence: 0.829708503333333

00:22:10.250 --> 00:22:11.776 stability across individuals, right.

NOTE Confidence: 0.829708503333333

00:22:11.776 --> 00:22:13.904 So we want to be confident that it's

NOTE Confidence: 0.829708503333333

00:22:13.904 --> 00:22:15.409 consistent across these six people,

NOTE Confidence: 0.829708503333333

00:22:15.410 --> 00:22:17.450 right, and that there's good coverage.

NOTE Confidence: 0.829708503333333

00:22:17.450 --> 00:22:19.610 Then we produce a single value single number,

NOTE Confidence: 0.829708503333333

00:22:19.610 --> 00:22:21.350 which is the average right

NOTE Confidence: 0.829708503333333

00:22:21.350 --> 00:22:22.742 across these six people.

NOTE Confidence: 0.829708503333333

00:22:22.750 --> 00:22:25.190 All the analysis are done on the data

NOTE Confidence: 0.829708503333333

00:22:25.190 --> 00:22:27.000 object that's you're seeing here,

NOTE Confidence: 0.829708503333333

00:22:27.000 --> 00:22:29.247 which is at the group parcel level.

NOTE Confidence: 0.829708503333333

00:22:29.250 --> 00:22:30.300 In other words,

NOTE Confidence: 0.829708503333333

00:22:30.300 --> 00:22:32.400 the principal component does not consider.

NOTE Confidence: 0.829708503333333

00:22:32.400 --> 00:22:33.798 Variation across people,

NOTE Confidence: 0.829708503333333

00:22:33.798 --> 00:22:36.128 it considers variation across areas,

NOTE Confidence: 0.829708503333333

00:22:36.130 --> 00:22:36.529 right,

NOTE Confidence: 0.829708503333333

00:22:36.529 --> 00:22:38.524 with the assumption obviously that

NOTE Confidence: 0.829708503333333

00:22:38.524 --> 00:22:40.120 people are consistently expressing

NOTE Confidence: 0.829708503333333

00:22:40.177 --> 00:22:42.067 these genes in these areas and

NOTE Confidence: 0.829708503333333

00:22:42.067 --> 00:22:43.327 that's an empirical question,

NOTE Confidence: 0.829708503333333

00:22:43.330 --> 00:22:43.594 right?

NOTE Confidence: 0.829708503333333

00:22:43.594 --> 00:22:45.442 One that we keep talking to NIH

NOTE Confidence: 0.829708503333333

00:22:45.442 --> 00:22:47.437 and the on human brain that was

NOTE Confidence: 0.829708503333333

00:22:47.437 --> 00:22:49.310 folks that they need more brains.

NOTE Confidence: 0.829708503333333

00:22:49.310 --> 00:22:51.830 They need to produce this kind of

NOTE Confidence: 0.829708503333333

00:22:51.830 --> 00:22:54.262 mapping a sample of sufficient size

NOTE Confidence: 0.829708503333333

00:22:54.262 --> 00:22:56.387 that we can interrogate whether

NOTE Confidence: 0.829708503333333

00:22:56.387 --> 00:22:58.968 there is true human variability.

NOTE Confidence: 0.829708503333333

00:22:58.970 --> 00:22:59.722 And furthermore,

NOTE Confidence: 0.829708503333333

00:22:59.722 --> 00:23:01.978 you could imagine this matters for

NOTE Confidence: 0.829708503333333

00:23:01.978 --> 00:23:03.906 psychedelic cardiology which is if your 5 HD.

NOTE Confidence: 0.829708503333333

00:23:03.910 --> 00:23:04.133 Receptors,

NOTE Confidence: 0.829708503333333

00:23:04.133 --> 00:23:05.694 which I'll talk about in a second,

NOTE Confidence: 0.829708503333333

00:23:05.700 --> 00:23:06.880 very differentiated across people.

NOTE Confidence: 0.829708503333333

00:23:06.880 --> 00:23:09.008 One could argue that some of the

NOTE Confidence: 0.829708503333333

00:23:09.008 --> 00:23:10.820 conclusions that will draw are incorrect,

NOTE Confidence: 0.829708503333333

00:23:10.820 --> 00:23:12.372 but I think you're,

NOTE Confidence: 0.829708503333333

00:23:12.372 --> 00:23:14.700 you're you're as always always go

NOTE Confidence: 0.829708503333333

00:23:14.776 --> 00:23:17.116 to the key intuition right away,

NOTE Confidence: 0.829708503333333

00:23:17.120 --> 00:23:19.376 which is that these maps are

NOTE Confidence: 0.829708503333333

00:23:19.376 --> 00:23:21.535 average across people and therefore

NOTE Confidence: 0.829708503333333

00:23:21.535 --> 00:23:23.284 limits generalizability across

NOTE Confidence: 0.829708503333333

00:23:23.284 --> 00:23:25.905 the the entire population, right.

NOTE Confidence: 0.829708503333333

00:23:25.905 --> 00:23:26.760 We don't know

NOTE Confidence: 0.70763251

00:23:26.940 --> 00:23:28.746 and also implies that your principal

NOTE Confidence: 0.70763251

00:23:28.746 --> 00:23:30.709 components are dependent on multiple genes.

NOTE Confidence: 0.70763251

00:23:30.710 --> 00:23:31.826 They're looking for patterns

NOTE Confidence: 0.70763251

00:23:31.826 --> 00:23:33.221 of multiple genes across areas

NOTE Confidence: 0.70763251

00:23:33.221 --> 00:23:34.898 they're not going to give. Exactly.

NOTE Confidence: 0.70763251

00:23:34.900 --> 00:23:37.294 Whereas if you had a much larger data set,

NOTE Confidence: 0.70763251

00:23:37.300 --> 00:23:38.956 you could look for components that

NOTE Confidence: 0.70763251

00:23:38.956 --> 00:23:40.749 are for grades within single genes,

NOTE Confidence: 0.70763251

00:23:40.750 --> 00:23:42.800 but you can't do that in this data set, so.

NOTE Confidence: 0.897958445555556

00:23:44.220 --> 00:23:45.014 Exactly, exactly.

NOTE Confidence: 0.897958445555556

00:23:45.014 --> 00:23:48.160 So you could ask the question of is

NOTE Confidence: 0.897958445555556

00:23:48.160 --> 00:23:51.040 there a gradient of a single gene across

NOTE Confidence: 0.897958445555556

00:23:51.040 --> 00:23:53.767 people in an area or across areas, right.

NOTE Confidence: 0.897958445555556

00:23:53.767 --> 00:23:55.452 That's another level of variance

NOTE Confidence: 0.897958445555556

00:23:55.452 --> 00:23:57.480 that is left on the table.

NOTE Confidence: 0.897958445555556

00:23:57.480 --> 00:23:58.748 But the first question,

NOTE Confidence: 0.897958445555556

00:23:58.748 --> 00:24:01.396 the only question really that we could ask

NOTE Confidence: 0.897958445555556

00:24:01.396 --> 00:24:03.419 was what's the spatial gradient, right?

NOTE Confidence: 0.897958445555556

00:24:03.419 --> 00:24:05.971 What is the spatial topography of the way

NOTE Confidence: 0.897958445555556

00:24:05.971 --> 00:24:08.300 these genes vary across cortical areas,

NOTE Confidence: 0.897958445555556

00:24:08.300 --> 00:24:11.380 right. And this is how they vary.

NOTE Confidence: 0.897958445555556

00:24:11.380 --> 00:24:13.908 And so it turns out that that explains

NOTE Confidence: 0.897958445555556

00:24:13.908 --> 00:24:15.700 almost 30% of all the variants, right?

NOTE Confidence: 0.897958445555556

00:24:15.700 --> 00:24:18.131 Not, not everything, but a lot, right?

NOTE Confidence: 0.897958445555556

00:24:18.131 --> 00:24:19.757 And so now you could say,

NOTE Confidence: 0.897958445555556

00:24:19.760 --> 00:24:21.098 oh, what does this look like?

NOTE Confidence: 0.897958445555556

00:24:21.100 --> 00:24:22.643 What kind of looks like Milan, right?

NOTE Confidence: 0.897958445555556

00:24:22.643 --> 00:24:24.418 So you could quantify that, right?

NOTE Confidence: 0.897958445555556

00:24:24.418 --> 00:24:27.220 And it turns out it looks a lot like my own.

NOTE Confidence: 0.897958445555556

00:24:27.220 --> 00:24:28.531 In other words,

NOTE Confidence: 0.897958445555556

00:24:28.531 --> 00:24:31.086 it varies along a hierarchy, right?

00:24:31.086 --> 00:24:33.648 Almost 1/3 of all the variants in

00:24:33.648 --> 00:24:36.088 human gene expression in the adult

00:24:36.088 --> 00:24:38.542 brains with this these six people

00:24:38.614 --> 00:24:40.909 varies along the principal axis,

00:24:40.910 --> 00:24:44.320 where it's high in sensory

00:24:44.320 --> 00:24:46.366 somatomotor or low.

00:24:46.370 --> 00:24:50.304 And low or high in association cortices,

00:24:50.310 --> 00:24:50.641 right?

00:24:50.641 --> 00:24:53.289 This is this gradient can go both ways,

00:24:53.290 --> 00:24:53.628 right?

00:24:53.628 --> 00:24:54.980 And this is cool,

00:24:54.980 --> 00:24:56.702 because now you can imagine this is

00:24:56.702 --> 00:24:58.649 the key way that the brain breaks,

00:24:58.650 --> 00:25:00.384 which is across this cortical hierarchy

00:25:00.384 --> 00:25:02.390 and its pattern of gene expression.

00:25:04.030 --> 00:25:07.124 Can you then look at what genes

NOTE Confidence: 0.865513212666667

00:25:07.124 --> 00:25:09.016 are contributing substantially to

NOTE Confidence: 0.865513212666667

00:25:09.016 --> 00:25:10.956 that first principal component?

NOTE Confidence: 0.865513212666667

00:25:10.960 --> 00:25:13.090 Because you would predict that,

NOTE Confidence: 0.865513212666667

00:25:13.090 --> 00:25:15.534 for example, oligodendrocyte genes

NOTE Confidence: 0.865513212666667

00:25:15.534 --> 00:25:17.367 might contribute significantly.

NOTE Confidence: 0.865513212666667

00:25:17.370 --> 00:25:19.220 So if oligodendrocyte genes covary

NOTE Confidence: 0.865513212666667

00:25:19.220 --> 00:25:21.429 with the myelin density map, that's.

NOTE Confidence: 0.865513212666667

00:25:21.429 --> 00:25:23.224 A different way of measuring

NOTE Confidence: 0.865513212666667

00:25:23.224 --> 00:25:24.660 exactly the same thing.

NOTE Confidence: 0.865513212666667

00:25:24.660 --> 00:25:26.011 It's not telling you something new as

NOTE Confidence: 0.865513212666667

00:25:26.011 --> 00:25:27.501 opposed to if there are other neural

NOTE Confidence: 0.865513212666667

00:25:27.501 --> 00:25:28.797 genes that might be less intuitive

NOTE Confidence: 0.865513212666667

00:25:28.841 --> 00:25:29.999 that they should vary and that

NOTE Confidence: 0.865513212666667

00:25:29.999 --> 00:25:31.266 might be telling you something new.

NOTE Confidence: 0.865513212666667

00:25:31.266 --> 00:25:32.967 So can you dig into the contributors

NOTE Confidence: 0.865513212666667

00:25:32.967 --> 00:25:34.522 to this component and start to

NOTE Confidence: 0.865513212666667

00:25:34.522 --> 00:25:35.782 make that kind of inference.

NOTE Confidence: 0.829545776190476

00:25:36.020 --> 00:25:37.952 Yeah of course you can check what's

NOTE Confidence: 0.829545776190476

00:25:37.952 --> 00:25:40.016 the loading of each gene onto this

NOTE Confidence: 0.829545776190476

00:25:40.016 --> 00:25:42.000 component and so on so definitely so.

NOTE Confidence: 0.829545776190476

00:25:42.000 --> 00:25:43.536 So I don't know if Josh has that

NOTE Confidence: 0.829545776190476

00:25:43.536 --> 00:25:44.988 in one of the tables are not

NOTE Confidence: 0.829545776190476

00:25:44.988 --> 00:25:46.549 in the paper but we can check.

NOTE Confidence: 0.829545776190476

00:25:46.550 --> 00:25:48.926 It's a really good question right and and

NOTE Confidence: 0.829545776190476

00:25:48.926 --> 00:25:51.049 allows for another access to exploration

NOTE Confidence: 0.829545776190476

00:25:51.049 --> 00:25:53.245 but the point that you're already.

NOTE Confidence: 0.829545776190476

00:25:53.250 --> 00:25:55.371 You know, your your questions and and

NOTE Confidence: 0.829545776190476

00:25:55.371 --> 00:25:56.670 suggestions are already highlighting

NOTE Confidence: 0.829545776190476

00:25:56.670 --> 00:25:58.698 this which is the cortical gene

NOTE Confidence: 0.829545776190476

00:25:58.698 --> 00:26:00.260 expression variation is dominated,

NOTE Confidence: 0.829545776190476

00:26:00.260 --> 00:26:02.390 right, by a single principle axis

NOTE Confidence: 0.829545776190476

00:26:02.390 --> 00:26:04.661 which is highly correlated with these

NOTE Confidence: 0.829545776190476

00:26:04.661 --> 00:26:07.013 expressions of hierarchy and that's great.

NOTE Confidence: 0.829545776190476

00:26:07.020 --> 00:26:08.980 OK, that's an observation, right.

NOTE Confidence: 0.829545776190476

00:26:08.980 --> 00:26:11.062 And these gradients of micro scale

NOTE Confidence: 0.829545776190476

00:26:11.062 --> 00:26:12.995 properties then can contribute perhaps

NOTE Confidence: 0.829545776190476

00:26:12.995 --> 00:26:14.959 to sensory association specialization,

NOTE Confidence: 0.829545776190476

00:26:14.960 --> 00:26:16.516 but furthermore may contribute

NOTE Confidence: 0.829545776190476

00:26:16.516 --> 00:26:18.461 to the effects of pharmacology

NOTE Confidence: 0.829545776190476

00:26:18.461 --> 00:26:20.525 across these cortical areas, right.

NOTE Confidence: 0.829545776190476

00:26:20.525 --> 00:26:23.360 And so this is this is work.

NOTE Confidence: 0.829545776190476

00:26:23.360 --> 00:26:25.106 That we've published on and actually

NOTE Confidence: 0.829545776190476

00:26:25.106 --> 00:26:26.997 I'm I'm also really proud of this

NOTE Confidence: 0.829545776190476

00:26:26.997 --> 00:26:28.874 John and I Co wrote a patient with

NOTE Confidence: 0.829545776190476

00:26:28.874 --> 00:26:30.404 our colleague Bill Martin who is

NOTE Confidence: 0.829545776190476

00:26:30.404 --> 00:26:33.066 now head of Global Neuro at J&amp;J

NOTE Confidence: 0.829545776190476

00:26:33.066 --> 00:26:34.860 and this was just recently awarded.

NOTE Confidence: 0.829545776190476

00:26:34.860 --> 00:26:36.124 So now we have a patent on this,

NOTE Confidence: 0.829545776190476

00:26:36.130 --> 00:26:38.374 not with that useful for anything

NOTE Confidence: 0.829545776190476

00:26:38.374 --> 00:26:40.640 but was it was something that we

NOTE Confidence: 0.829545776190476

00:26:40.640 --> 00:26:42.555 wanted to develop and really kind

NOTE Confidence: 0.829545776190476

00:26:42.555 --> 00:26:46.210 of drive forward anyway so.

NOTE Confidence: 0.829545776190476

00:26:46.210 --> 00:26:47.476 Sharp left turn.

NOTE Confidence: 0.829545776190476

00:26:47.476 --> 00:26:50.008 How does this relate to pharmacological

NOTE Confidence: 0.829545776190476

00:26:50.008 --> 00:26:52.310 effects of any kind and psychedelic

NOTE Confidence: 0.829545776190476

00:26:52.310 --> 00:26:53.930 psychedelics in particular?

NOTE Confidence: 0.829545776190476

00:26:53.930 --> 00:26:55.266 You guys are probably thinking when is he

NOTE Confidence: 0.829545776190476

00:26:55.266 --> 00:26:56.847 going to get to anything psychedelic related?

NOTE Confidence: 0.829545776190476

00:26:56.850 --> 00:26:58.194 Like why am I listening to this?

NOTE Confidence: 0.829545776190476

00:26:58.200 --> 00:27:02.990 So, so we're we're getting there, so.

NOTE Confidence: 0.829545776190476

00:27:02.990 --> 00:27:06.732 OK, this map and and I had some

NOTE Confidence: 0.829545776190476

00:27:06.732 --> 00:27:07.824 set up slides, but,

NOTE Confidence: 0.829545776190476

00:27:07.824 --> 00:27:09.390 but I actually want to go a little faster,

NOTE Confidence: 0.829545776190476

00:27:09.390 --> 00:27:09.736 right.

NOTE Confidence: 0.829545776190476

00:27:09.736 --> 00:27:12.158 So this is a paper published by

NOTE Confidence: 0.829545776190476

00:27:12.158 --> 00:27:14.688 Katrine in elife a couple years ago,

NOTE Confidence: 0.829545776190476

00:27:14.690 --> 00:27:15.070 right.

NOTE Confidence: 0.829545776190476

00:27:15.070 --> 00:27:17.350 And So what she's done is

NOTE Confidence: 0.829545776190476

00:27:17.350 --> 00:27:21.498 basically giving people a.

NOTE Confidence: 0.829545776190476

00:27:21.500 --> 00:27:25.343 A pill of LSD which targets the

NOTE Confidence: 0.829545776190476

00:27:25.343 --> 00:27:27.860 serotonin receptor versus placebo.

NOTE Confidence: 0.829545776190476

00:27:27.860 --> 00:27:30.114 And what we've done is we've computed

NOTE Confidence: 0.829545776190476

00:27:30.114 --> 00:27:32.973 a map of unresting state of the effect

NOTE Confidence: 0.829545776190476

00:27:32.973 --> 00:27:35.980 of LSD on every single person and this

NOTE Confidence: 0.829545776190476

00:27:35.980 --> 00:27:38.577 is the average across all the people,

NOTE Confidence: 0.829545776190476

00:27:38.580 --> 00:27:40.710 right?

NOTE Confidence: 0.829545776190476

00:27:40.710 --> 00:27:43.464 In the effects of LSD on a metric that

NOTE Confidence: 0.829545776190476

00:27:43.464 --> 00:27:46.167 we call global brain connectivity.

NOTE Confidence: 0.829545776190476

00:27:46.170 --> 00:27:47.818 So let me unpack this a little bit

NOTE Confidence: 0.829545776190476

00:27:47.818 --> 00:27:49.698 so you so you develop an intuition.

NOTE Confidence: 0.829545776190476

00:27:49.700 --> 00:27:52.395 Every warm area that you see here

NOTE Confidence: 0.829545776190476

00:27:52.395 --> 00:27:55.667 is an area that has an elevation

NOTE Confidence: 0.829545776190476

00:27:55.667 --> 00:27:58.197 in its brain wide covariation.

NOTE Confidence: 0.829545776190476

00:27:58.200 --> 00:28:00.318 When people are given LSD relative

NOTE Confidence: 0.829545776190476

00:28:00.318 --> 00:28:02.512 to cell cycle, so in other words,

NOTE Confidence: 0.829545776190476

00:28:02.512 --> 00:28:04.210 you could you could say it's

NOTE Confidence: 0.829545776190476

00:28:04.274 --> 00:28:05.738 a hyperconnectivity, right?

NOTE Confidence: 0.829545776190476

00:28:05.738 --> 00:28:07.802 But I don't like to use that term

NOTE Confidence: 0.829545776190476

00:28:07.802 --> 00:28:09.517 before impacting it first, right?

NOTE Confidence: 0.829545776190476

00:28:09.517 --> 00:28:10.558 So for instance,

NOTE Confidence: 0.829545776190476

00:28:10.558 --> 00:28:14.090 the visual cortex here would.

NOTE Confidence: 0.829545776190476

00:28:14.090 --> 00:28:16.500 This the interpretation is that

NOTE Confidence: 0.829545776190476

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00:28:16.500 --> 00:28:18.823 LSD elevates the connectivity with

NOTE Confidence: 0.829545776190476

00:28:18.823 --> 00:28:21.980 the rest of the brain for visual

NOTE Confidence: 0.829545776190476

00:28:22.068 --> 00:28:24.908 cortex bilaterally and for sensory

NOTE Confidence: 0.829545776190476

00:28:24.910 --> 00:28:27.618 somatomotor cortex and MTV.

NOTE Confidence: 0.829545776190476

00:28:27.618 --> 00:28:30.976 But it reduces connectivity in

NOTE Confidence: 0.829545776190476

00:28:30.976 --> 00:28:33.560 these association areas, right?

NOTE Confidence: 0.829545776190476

00:28:33.560 --> 00:28:34.820 So this is important, right?

NOTE Confidence: 0.829545776190476

00:28:34.820 --> 00:28:35.975 In other words,

NOTE Confidence: 0.829545776190476

00:28:35.975 --> 00:28:37.900 there is a bidirectional effect

NOTE Confidence: 0.829545776190476

00:28:37.900 --> 00:28:40.874 of LSD versus placebo on sensory

NOTE Confidence: 0.829545776190476

00:28:40.874 --> 00:28:42.871 versus association regions, right?

NOTE Confidence: 0.829545776190476

00:28:42.871 --> 00:28:44.737 At least it appears that way,

NOTE Confidence: 0.918407525

00:28:44.740 --> 00:28:48.753 right? And so we can now isolate the Type

NOTE Confidence: 0.918407525

00:28:48.753 --> 00:28:51.560 1 error protected effect right by doing

NOTE Confidence: 0.918407525

00:28:51.633 --> 00:28:54.566 TFCC protection at the whole brain level.

NOTE Confidence: 0.918407525

00:28:54.570 --> 00:28:56.845 And now you can see this values,

NOTE Confidence: 0.918407525

00:28:56.850 --> 00:28:59.132 this is what's pulling out the values

NOTE Confidence: 0.918407525

00:28:59.132 --> 00:29:02.198 out of this area now what Katrina has

NOTE Confidence: 0.918407525

00:29:02.198 --> 00:29:04.990 also done which is. Pretty clever.

NOTE Confidence: 0.918407525

00:29:04.990 --> 00:29:08.246 She's given people ketanserin prior to the

NOTE Confidence: 0.918407525

00:29:08.246 --> 00:29:10.598 administration of LSD right and contains.

NOTE Confidence: 0.918407525

00:29:10.600 --> 00:29:14.040 Azrin is thought to be a very selective

NOTE Confidence: 0.918407525

00:29:14.040 --> 00:29:16.927 antagonist of the five HT 2A receptor.

NOTE Confidence: 0.918407525

00:29:16.930 --> 00:29:18.994 And you'll notice that when people

NOTE Confidence: 0.918407525

00:29:18.994 --> 00:29:20.370 are pretreated with ketanserin,

NOTE Confidence: 0.918407525

00:29:20.370 --> 00:29:23.458 they look just like.

NOTE Confidence: 0.918407525

00:29:23.460 --> 00:29:24.012 Placebo right.

NOTE Confidence: 0.918407525

00:29:24.012 --> 00:29:24.840 In other words,

NOTE Confidence: 0.918407525

00:29:24.840 --> 00:29:26.694 there is no effect of LSD in those areas.

NOTE Confidence: 0.918407525

00:29:26.700 --> 00:29:28.884 And this is true for the areas that

NOTE Confidence: 0.918407525

00:29:28.884 --> 00:29:30.631 show a reduction in connectivity

NOTE Confidence: 0.918407525

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00:29:30.631 --> 00:29:33.270 by LSD and the regions that show

NOTE Confidence: 0.918407525

00:29:33.341 --> 00:29:35.615 an increase in connectivity by LSD.

NOTE Confidence: 0.918407525

00:29:35.620 --> 00:29:38.374 So there is a full blockade of the effect

NOTE Confidence: 0.918407525

00:29:38.374 --> 00:29:41.444 of LSD by Captain Strand on average, right?

NOTE Confidence: 0.918407525

00:29:41.444 --> 00:29:43.434 So that's pretty cool, right.

NOTE Confidence: 0.918407525

00:29:43.434 --> 00:29:46.620 And and I remember showing this to to John

NOTE Confidence: 0.918407525

00:29:46.694 --> 00:29:49.638 Crystal years ago when we first saw this

NOTE Confidence: 0.918407525

00:29:49.638 --> 00:29:52.618 effect and saying like look the two maps,

NOTE Confidence: 0.918407525

00:29:52.620 --> 00:29:54.690 the LSD versus placebo and the

NOTE Confidence: 0.918407525

00:29:54.690 --> 00:29:56.544 LSD plus captain string versus

NOTE Confidence: 0.918407525

00:29:56.544 --> 00:29:58.180 LSD are super correlated.

NOTE Confidence: 0.918407525

00:29:58.180 --> 00:29:59.860 Look, they're almost the same.

NOTE Confidence: 0.918407525

00:29:59.860 --> 00:30:01.939 And and I'll show you what they

NOTE Confidence: 0.918407525

00:30:01.939 --> 00:30:03.808 look like side by side, right.

NOTE Confidence: 0.918407525

00:30:03.808 --> 00:30:06.506 This is same people, two different days.

NOTE Confidence: 0.918407525

00:30:06.506 --> 00:30:08.416 One day they're given LSD

NOTE Confidence: 0.918407525

00:30:08.416 --> 00:30:09.780 alone versus placebo,

NOTE Confidence: 0.918407525

00:30:09.780 --> 00:30:11.240 the other day they're given

NOTE Confidence: 0.918407525

00:30:11.240 --> 00:30:12.408 contains trend prior to.

NOTE Confidence: 0.918407525

00:30:12.410 --> 00:30:16.057 Was the and then contrasted to placebo.

NOTE Confidence: 0.918407525

00:30:16.060 --> 00:30:17.398 And I'm like, this is incredible.

NOTE Confidence: 0.918407525

00:30:17.400 --> 00:30:18.020 They look the same.

NOTE Confidence: 0.918407525

00:30:18.020 --> 00:30:18.950 And he just laughed at me.

NOTE Confidence: 0.918407525

00:30:18.950 --> 00:30:19.758 He was like, ohh,

NOTE Confidence: 0.918407525

00:30:19.758 --> 00:30:20.566 of course it's pharmacology.

NOTE Confidence: 0.918407525

00:30:20.570 --> 00:30:21.694 It has to be.

NOTE Confidence: 0.918407525

00:30:21.694 --> 00:30:22.256 Was like,

NOTE Confidence: 0.918407525

00:30:22.260 --> 00:30:22.500 well,

NOTE Confidence: 0.918407525

00:30:22.500 --> 00:30:24.420 I'm so glad it's so obvious to you

NOTE Confidence: 0.918407525

00:30:24.420 --> 00:30:26.700 that that you're going to get such a

NOTE Confidence: 0.918407525

00:30:26.700 --> 00:30:28.331 correspondence in the within subject

NOTE Confidence: 0.918407525

00:30:28.331 --> 00:30:30.146 effect of pharmacological effects on

NOTE Confidence: 0.918407525

00:30:30.146 --> 00:30:32.143 brain imaging at the surface level.

NOTE Confidence: 0.918407525

00:30:32.143 --> 00:30:33.949 Like I wouldn't have guessed that,

NOTE Confidence: 0.918407525

00:30:33.950 --> 00:30:36.110 right, but this is important,

NOTE Confidence: 0.918407525

00:30:36.110 --> 00:30:36.489 right,

NOTE Confidence: 0.918407525

00:30:36.489 --> 00:30:38.763 because it highlights that we can

NOTE Confidence: 0.918407525

00:30:38.763 --> 00:30:40.300 leverage surface based topography

NOTE Confidence: 0.918407525

00:30:40.300 --> 00:30:42.617 as an index of the effect of

NOTE Confidence: 0.918407525

00:30:42.617 --> 00:30:44.696 pharmacology on the human brain, right.

NOTE Confidence: 0.918407525

00:30:44.696 --> 00:30:47.784 And so now, now we get this map,

NOTE Confidence: 0.918407525

00:30:47.790 --> 00:30:50.390 this delta map, delta GBC,

NOTE Confidence: 0.918407525

00:30:50.390 --> 00:30:52.050 right and now we ask.

NOTE Confidence: 0.918407525

00:30:52.050 --> 00:30:54.120 OK, what about gene expression patterns,

NOTE Confidence: 0.918407525

00:30:54.120 --> 00:30:54.408 right?

NOTE Confidence: 0.918407525

00:30:54.408 --> 00:30:56.424 If this is truly related to the

NOTE Confidence: 0.918407525

00:30:56.424 --> 00:30:58.360 serotonin 5H2 receptor which we

NOTE Confidence: 0.918407525

00:30:58.360 --> 00:31:00.410 believe contains from this blocking?

NOTE Confidence: 0.918407525

00:31:00.410 --> 00:31:02.816 Then presumably the 5H2 receptor map

NOTE Confidence: 0.918407525

00:31:02.816 --> 00:31:05.420 ought to look like this map, right?

NOTE Confidence: 0.918407525

00:31:05.420 --> 00:31:06.770 So that's what we tried.

NOTE Confidence: 0.918407525

00:31:06.770 --> 00:31:08.330 We took the gene expression map,

NOTE Confidence: 0.918407525

00:31:08.330 --> 00:31:08.730 right,

NOTE Confidence: 0.918407525

00:31:08.730 --> 00:31:10.730 and we computed the correlation

NOTE Confidence: 0.918407525

00:31:10.730 --> 00:31:12.707 right across these two, right.

NOTE Confidence: 0.918407525

00:31:12.707 --> 00:31:15.723 And we also took some other target genes,

NOTE Confidence: 0.918407525

00:31:15.730 --> 00:31:16.246 right,

NOTE Confidence: 0.918407525

00:31:16.246 --> 00:31:19.342 that are thought in the literature

NOTE Confidence: 0.918407525

00:31:19.342 --> 00:31:21.629 to be targeted by LSD.

NOTE Confidence: 0.918407525

00:31:21.630 --> 00:31:24.206 And then we computed a similarity of

NOTE Confidence: 0.918407525

00:31:24.206 --> 00:31:26.257 correlation between this and this is

NOTE Confidence: 0.918407525

00:31:26.257 --> 00:31:28.033 serotonin is right up here, right.

NOTE Confidence: 0.918407525

00:31:28.033 --> 00:31:30.876 So it's the of these, it's the most.

NOTE Confidence: 0.918407525

00:31:30.876 --> 00:31:31.760 Positively correlated.

NOTE Confidence: 0.918407525

00:31:31.760 --> 00:31:34.147 And then we repeated this for the

NOTE Confidence: 0.918407525

00:31:34.147 --> 00:31:35.891 entire distribution of all genes

NOTE Confidence: 0.918407525

00:31:35.891 --> 00:31:37.853 from the alien human brain Atlas.

NOTE Confidence: 0.918407525

00:31:37.860 --> 00:31:38.732 And again,

NOTE Confidence: 0.918407525

00:31:38.732 --> 00:31:41.350 serotonin comes out here in the

NOTE Confidence: 0.918407525

00:31:41.350 --> 00:31:43.704 95th at almost 96 percentile, right?

NOTE Confidence: 0.918407525

00:31:43.704 --> 00:31:44.748 So there are some things that

NOTE Confidence: 0.918407525

00:31:44.748 --> 00:31:45.270 by chance could

NOTE Confidence: 0.833545896666667

00:31:45.305 --> 00:31:46.796 be higher, but this is pretty.

NOTE Confidence: 0.833545896666667

00:31:46.796 --> 00:31:48.530 Encouraging as a initial proof of

NOTE Confidence: 0.833545896666667

00:31:48.587 --> 00:31:50.519 principle that we can actually map

NOTE Confidence: 0.833545896666667

00:31:50.519 --> 00:31:52.193 human gene expression in relation

NOTE Confidence: 0.833545896666667

00:31:52.193 --> 00:31:53.853 to the pharmacological effects on

NOTE Confidence: 0.833545896666667

00:31:53.853 --> 00:31:56.982 the human brain in vivo of a given

NOTE Confidence: 0.833545896666667

00:31:56.982 --> 00:31:59.670 pharmacological agent that was blocked by

NOTE Confidence: 0.833545896666667

00:31:59.757 --> 00:32:03.132 the hypothesized receptor antagonist, right?

NOTE Confidence: 0.833545896666667

00:32:03.132 --> 00:32:05.904 That's in my mind pretty cool.

NOTE Confidence: 0.833545896666667

00:32:05.910 --> 00:32:08.790 And so, so you also see the opposite,

NOTE Confidence: 0.833545896666667

00:32:08.790 --> 00:32:10.966 which is HR7, which in my mind has

NOTE Confidence: 0.833545896666667

00:32:10.966 --> 00:32:13.130 some very interesting pharmacology,

NOTE Confidence: 0.833545896666667

00:32:13.130 --> 00:32:14.813 but we won't get into that today, right?

NOTE Confidence: 0.833545896666667

00:32:14.813 --> 00:32:16.794 It's just you also see the opposite

NOTE Confidence: 0.833545896666667

00:32:16.794 --> 00:32:19.306 effects in this, this kind of analysis.

NOTE Confidence: 0.833545896666667

00:32:19.306 --> 00:32:22.968 OK. So. How do we take

NOTE Confidence: 0.860314308571429

00:32:22.980 --> 00:32:24.120 this quick question?

NOTE Confidence: 0.860314308571429

00:32:24.120 --> 00:32:26.696 If you go back, I'm thinking about

NOTE Confidence: 0.860314308571429

00:32:26.696 --> 00:32:28.808 the 1A receptor which is usually

NOTE Confidence: 0.860314308571429

00:32:28.808 --> 00:32:30.957 pre synaptic on Axon terminals,

NOTE Confidence: 0.860314308571429

00:32:30.960 --> 00:32:33.534 which means that the receptor is

NOTE Confidence: 0.860314308571429

00:32:33.534 --> 00:32:37.036 not in the same place as the M RNA.

NOTE Confidence: 0.860314308571429

00:32:37.040 --> 00:32:39.484 That's what you're doing here.

NOTE Confidence: 0.860314308571429

00:32:39.484 --> 00:32:41.393 When you're when you're looking at the

NOTE Confidence: 0.860314308571429

00:32:41.393 --> 00:32:42.883 distribution of gene expression across

NOTE Confidence: 0.860314308571429

00:32:42.883 --> 00:32:45.320 the brain, you're looking at M RNA,

NOTE Confidence: 0.860314308571429

00:32:45.320 --> 00:32:48.736 which is basically where the cell bodies.

NOTE Confidence: 0.860314308571429

00:32:48.740 --> 00:32:52.075 Right and. That should be pretty good

NOTE Confidence: 0.860314308571429

00:32:52.075 --> 00:32:53.220 because it's amended and Reddick.

NOTE Confidence: 0.860314308571429

00:32:53.220 --> 00:32:54.648 But for the 1A receptor there,

NOTE Confidence: 0.860314308571429

00:32:54.650 --> 00:32:56.750 there's going to be a substantial

NOTE Confidence: 0.860314308571429

00:32:56.750 --> 00:32:58.451 dissociation between where the M

NOTE Confidence: 0.860314308571429

00:32:58.451 --> 00:33:00.124 RNA is and where the receptor is,

NOTE Confidence: 0.860314308571429

00:33:00.130 --> 00:33:01.124 which I don't think you can get

NOTE Confidence: 0.860314308571429

00:33:01.124 --> 00:33:01.930 it at this technique.

NOTE Confidence: 0.860314308571429

00:33:01.930 --> 00:33:04.098 So just for some receptors that may be

NOTE Confidence: 0.5617697675

00:33:04.200 --> 00:33:06.188 applicant, you're absolutely right.

NOTE Confidence: 0.5617697675

00:33:06.190 --> 00:33:08.058 So you're absolutely right.

NOTE Confidence: 0.5617697675

00:33:08.058 --> 00:33:10.690 So what you're highlighting is the nuance,

NOTE Confidence: 0.5617697675

00:33:10.690 --> 00:33:12.560 the Super important nuance between

NOTE Confidence: 0.5617697675

00:33:12.560 --> 00:33:14.634 the ligand and the receptor, right.

NOTE Confidence: 0.5617697675

00:33:14.634 --> 00:33:16.266 And basically the fact that the M RNA

NOTE Confidence: 0.5617697675

00:33:16.266 --> 00:33:17.907 may be coding for the ligand or the

NOTE Confidence: 0.5617697675

00:33:17.907 --> 00:33:19.512 receptor and in the cases where it's

NOTE Confidence: 0.5617697675

00:33:19.512 --> 00:33:21.560 coding for the receptor, this analysis.

NOTE Confidence: 0.5617697675

00:33:21.560 --> 00:33:23.986 Approach may be very informative,

NOTE Confidence: 0.5617697675

00:33:23.986 --> 00:33:25.462 but in the cases where it's

NOTE Confidence: 0.5617697675

00:33:25.462 --> 00:33:26.560 coding for the ligand,

NOTE Confidence: 0.5617697675

00:33:26.560 --> 00:33:27.750 it may or may not be informative.

NOTE Confidence: 0.780933518571429

00:33:27.760 --> 00:33:29.097 It's not about whether it's the ligand,

NOTE Confidence: 0.780933518571429

00:33:29.100 --> 00:33:33.484 it's where the receptor is on the neuron.

NOTE Confidence: 0.780933518571429

00:33:33.490 --> 00:33:36.170 So for pre, for pre synaptic receptors,

NOTE Confidence: 0.780933518571429

00:33:36.170 --> 00:33:37.214 for receptors that are

NOTE Confidence: 0.780933518571429

00:33:37.214 --> 00:33:38.795 targeted to Axon terminals,

NOTE Confidence: 0.780933518571429

00:33:38.795 --> 00:33:40.784 we see this in the animal literature

NOTE Confidence: 0.780933518571429

00:33:40.784 --> 00:33:41.996 all the time where the receptor

NOTE Confidence: 0.780933518571429

00:33:41.996 --> 00:33:43.305 in the M RNA are in different

NOTE Confidence: 0.780933518571429

00:33:43.305 --> 00:33:44.367 places because the receptor is

NOTE Confidence: 0.780933518571429

00:33:44.367 --> 00:33:45.609 way out on the Axon terminals,

NOTE Confidence: 0.780933518571429

00:33:45.610 --> 00:33:47.563 which is in a different part of

NOTE Confidence: 0.780933518571429

00:33:47.563 --> 00:33:49.310 the brain from the cell body.

NOTE Confidence: 0.780933518571429

00:33:49.310 --> 00:33:50.330 It's not about the ligand,

NOTE Confidence: 0.780933518571429

00:33:50.330 --> 00:33:51.825 it's about where the receptor

NOTE Confidence: 0.780933518571429

00:33:51.825 --> 00:33:53.320 is localized in the neuron.

NOTE Confidence: 0.714856385

00:33:53.450 --> 00:33:54.770 So you're highlighting something

NOTE Confidence: 0.714856385

00:33:54.770 --> 00:33:56.374 even different, right, which is which

NOTE Confidence: 0.714856385

00:33:56.374 --> 00:33:57.790 is now beginning to appreciate it.

NOTE Confidence: 0.714856385

00:33:57.790 --> 00:34:00.748 So you're saying that the postsynaptic

00:34:00.748 --> 00:34:03.410 receptor expression of the five HD.

00:34:03.410 --> 00:34:06.566 Way. Is potentially captured very well

00:34:06.566 --> 00:34:11.745 by the M RNA and the the the probes

00:34:11.745 --> 00:34:15.285 whereas the presynaptic 1A may may be a

00:34:15.285 --> 00:34:17.040 very different phenomenon because it's

00:34:17.111 --> 00:34:19.386 on the presynaptic terminals right.

00:34:19.390 --> 00:34:21.308 And therefore you're not binding to it.

00:34:21.310 --> 00:34:23.415 And then furthermore furthermore it's

00:34:23.415 --> 00:34:26.330 this is where my thinking was going

00:34:26.330 --> 00:34:28.927 which is the ligand versus the receptor,

00:34:28.930 --> 00:34:30.953 right because now you have that third

00:34:30.953 --> 00:34:33.454 axis of variation and so and and to your

00:34:33.454 --> 00:34:34.980 point this gets complicated because.

00:34:34.980 --> 00:34:37.636 When you give a substance like a psychedelic,

00:34:37.640 --> 00:34:39.446 you have post,

00:34:39.446 --> 00:34:42.898 you have polysynaptic distal effects, right?

NOTE Confidence: 0.714856385

00:34:42.898 --> 00:34:46.402 Which is it's going to travel right through

NOTE Confidence: 0.714856385

00:34:46.402 --> 00:34:50.009 the Axon and potentially shuttle onto the.

NOTE Confidence: 0.714856385

00:34:50.010 --> 00:34:51.990 Receptors and activate those terminals

NOTE Confidence: 0.714856385

00:34:51.990 --> 00:34:54.971 on distal neurons that are not in the

NOTE Confidence: 0.714856385

00:34:54.971 --> 00:34:57.148 local tissue bed of the high expression,

NOTE Confidence: 0.714856385

00:34:57.150 --> 00:34:59.460 which is why and this is actually

NOTE Confidence: 0.714856385

00:34:59.460 --> 00:35:01.396 gets really nuanced why looking at

NOTE Confidence: 0.714856385

00:35:01.396 --> 00:35:03.883 the dense GBC at the voxel level and

NOTE Confidence: 0.714856385

00:35:03.883 --> 00:35:05.753 partially the GBC doesn't necessarily

NOTE Confidence: 0.714856385

00:35:05.753 --> 00:35:08.970 fully map onto one another because that

NOTE Confidence: 0.714856385

00:35:08.970 --> 00:35:11.226 level of granularity begins to matter,

NOTE Confidence: 0.714856385

00:35:11.230 --> 00:35:11.496 right.

NOTE Confidence: 0.714856385

00:35:11.496 --> 00:35:13.092 And you can now appreciate right

NOTE Confidence: 0.714856385

00:35:13.092 --> 00:35:14.823 that if you are averaging signal

NOTE Confidence: 0.714856385

00:35:14.823 --> 00:35:16.867 within an area or if you're looking

NOTE Confidence: 0.714856385

00:35:16.925 --> 00:35:18.437 at boxing level pharmacology,

NOTE Confidence: 0.714856385

00:35:18.440 --> 00:35:20.408 right and furthermore if you can.

NOTE Confidence: 0.714856385

00:35:20.410 --> 00:35:21.810 Some even deeper into

NOTE Confidence: 0.714856385

00:35:21.810 --> 00:35:22.860 columnar level pharmacology,

NOTE Confidence: 0.714856385

00:35:22.860 --> 00:35:25.342 but they're an important ones here, right?

NOTE Confidence: 0.714856385

00:35:25.342 --> 00:35:27.994 But at the very coarse level,

NOTE Confidence: 0.714856385

00:35:28.000 --> 00:35:29.740 you can at least begin to

NOTE Confidence: 0.714856385

00:35:29.740 --> 00:35:30.900 identify these first principles,

NOTE Confidence: 0.714856385

00:35:30.900 --> 00:35:32.760 which is pharmacological

NOTE Confidence: 0.714856385

00:35:32.760 --> 00:35:35.240 neuroimaging topographies with GBC,

NOTE Confidence: 0.714856385

00:35:35.240 --> 00:35:37.019 which is this random freaking measure, right?

NOTE Confidence: 0.714856385

00:35:37.019 --> 00:35:39.164 That that seemingly has these

NOTE Confidence: 0.714856385

00:35:39.164 --> 00:35:41.904 properties that we really like maps

NOTE Confidence: 0.714856385

00:35:41.904 --> 00:35:44.045 onto gene expression gradients, right?

NOTE Confidence: 0.714856385

00:35:44.045 --> 00:35:45.515 Like who would have thunk it?

NOTE Confidence: 0.714856385

00:35:45.520 --> 00:35:46.357 And it's not.

NOTE Confidence: 0.714856385

00:35:46.357 --> 00:35:48.310 And and the important thing about this

NOTE Confidence: 0.714856385

00:35:48.368 --> 00:35:50.511 is that if you use some graph, theoretical.

NOTE Confidence: 0.714856385

00:35:50.511 --> 00:35:51.042 Distraction.

NOTE Confidence: 0.714856385

00:35:51.042 --> 00:35:53.166 Without a surface map,

NOTE Confidence: 0.714856385

00:35:53.170 --> 00:35:54.742 there's no freaking way you can

NOTE Confidence: 0.714856385

00:35:54.742 --> 00:35:55.528 get this right.

NOTE Confidence: 0.714856385

00:35:55.530 --> 00:35:57.546 And that's actually kind of the take

NOTE Confidence: 0.714856385

00:35:57.546 --> 00:36:00.061 away that I was trying to get at right

NOTE Confidence: 0.714856385

00:36:00.061 --> 00:36:02.264 is that that this is obscured if you

NOTE Confidence: 0.714856385

00:36:02.264 --> 00:36:04.244 do not have a surface map, right?

NOTE Confidence: 0.714856385

00:36:04.244 --> 00:36:06.927 You just can never see it, Umm,

NOTE Confidence: 0.714856385

00:36:06.927 --> 00:36:09.712 because that's what drives the

NOTE Confidence: 0.714856385

00:36:09.712 --> 00:36:12.070 correspondence, right, and the location.

NOTE Confidence: 0.714856385

00:36:12.070 --> 00:36:13.430 So anyway, so, so,

NOTE Confidence: 0.714856385

00:36:13.430 --> 00:36:15.809 so now I I want to be sensitive to time,

00:36:15.810 --> 00:36:16.834 so I may have to kind of speed

00:36:16.834 --> 00:36:17.807 up to some of this stuff.

00:36:17.810 --> 00:36:20.010 So, so basically the point of this is

00:36:20.010 --> 00:36:22.690 how do we map this onto neurobehavioral,

00:36:22.690 --> 00:36:25.575 geometric models in in clinical

00:36:25.575 --> 00:36:27.306 population level analysis,

00:36:27.310 --> 00:36:27.616 right.

00:36:27.616 --> 00:36:29.452 And so this cartoon is just

00:36:29.452 --> 00:36:30.743 highlighting that there's some

00:36:30.743 --> 00:36:32.348 brain to behavioral relationship and

00:36:32.348 --> 00:36:34.349 that it's probably or some oblique,

00:36:34.350 --> 00:36:35.378 maybe even not linear.

00:36:35.378 --> 00:36:37.140 And we don't know what it is.

00:36:37.140 --> 00:36:41.048 And so this is work really purely done

00:36:41.048 --> 00:36:43.452 by my former student now research

00:36:43.452 --> 00:36:45.017 scientist here in our department,

NOTE Confidence: 0.714856385

00:36:45.020 --> 00:36:47.805 Lisa and and she's published

NOTE Confidence: 0.714856385

00:36:47.805 --> 00:36:51.210 this in life earlier last year.

NOTE Confidence: 0.714856385

00:36:51.210 --> 00:36:53.370 After a whole saga.

NOTE Confidence: 0.714856385

00:36:53.370 --> 00:36:53.910 So,

NOTE Confidence: 0.714856385

00:36:53.910 --> 00:36:55.820 so I I I want to this gets a little

NOTE Confidence: 0.767347726363636

00:36:55.882 --> 00:36:58.278 technical, so I'll try to kind of keep

NOTE Confidence: 0.767347726363636

00:36:58.278 --> 00:37:00.925 it clear and then get to the key points.

NOTE Confidence: 0.767347726363636

00:37:00.930 --> 00:37:03.354 So if we're going to leverage

NOTE Confidence: 0.767347726363636

00:37:03.354 --> 00:37:04.970 pharmacological new imaging that's

NOTE Confidence: 0.767347726363636

00:37:05.041 --> 00:37:07.237 even benchmark with gene expression or

NOTE Confidence: 0.767347726363636

00:37:07.237 --> 00:37:09.880 what have you right to achieve brain

NOTE Confidence: 0.767347726363636

00:37:09.880 --> 00:37:12.220 behavioral models that can actually be

NOTE Confidence: 0.767347726363636

00:37:12.220 --> 00:37:14.388 deployed for any therapeutic purpose.

NOTE Confidence: 0.767347726363636

00:37:14.390 --> 00:37:16.398 There are some criteria that I'd like to

NOTE Confidence: 0.767347726363636

00:37:16.398 --> 00:37:18.744 argue we need to really hold in mind, right.

NOTE Confidence: 0.767347726363636

00:37:18.744 --> 00:37:21.496 And these criteria are are not exhaustive and

NOTE Confidence: 0.767347726363636

00:37:21.496 --> 00:37:24.006 things that I've learned the hard way that,

NOTE Confidence: 0.767347726363636

00:37:24.010 --> 00:37:26.040 you know, if you don't do this,

NOTE Confidence: 0.767347726363636

00:37:26.040 --> 00:37:27.060 things are just brittle.

NOTE Confidence: 0.767347726363636

00:37:27.060 --> 00:37:28.590 So the first one is more

NOTE Confidence: 0.767347726363636

00:37:28.649 --> 00:37:30.107 kind of for the whole field,

NOTE Confidence: 0.767347726363636

00:37:30.110 --> 00:37:32.270 which is that anything that we

NOTE Confidence: 0.767347726363636

00:37:32.270 --> 00:37:35.482 produce as a field has to scale and

NOTE Confidence: 0.767347726363636

00:37:35.482 --> 00:37:37.602 interoperate in an informatics way.

NOTE Confidence: 0.767347726363636

00:37:37.610 --> 00:37:38.537 So for instance,

NOTE Confidence: 0.767347726363636

00:37:38.537 --> 00:37:40.700 what Pronet is doing and what Professor

NOTE Confidence: 0.767347726363636

00:37:40.764 --> 00:37:42.913 Woods is doing in our department with

NOTE Confidence: 0.767347726363636

00:37:42.913 --> 00:37:44.520 this massive worldwide consortium.

NOTE Confidence: 0.767347726363636

00:37:44.520 --> 00:37:45.015 Right.

NOTE Confidence: 0.767347726363636

00:37:45.015 --> 00:37:48.670 So, so the days of me working on my PC

NOTE Confidence: 0.767347726363636

00:37:48.670 --> 00:37:50.603 and producing imaging are gone, right?

NOTE Confidence: 0.767347726363636

00:37:50.603 --> 00:37:52.418 Like it's no longer that.

NOTE Confidence: 0.767347726363636

00:37:52.420 --> 00:37:55.470 So then the measure selection,

NOTE Confidence: 0.767347726363636

00:37:55.470 --> 00:37:57.626 and I mean the behavioral measure selection

NOTE Confidence: 0.767347726363636

00:37:57.626 --> 00:37:59.478 matters here and it matters a lot.

NOTE Confidence: 0.767347726363636

00:37:59.480 --> 00:38:01.588 And I'll show you why. Then.

NOTE Confidence: 0.767347726363636

00:38:01.588 --> 00:38:04.456 How do we cross validate those

NOTE Confidence: 0.767347726363636

00:38:04.456 --> 00:38:05.412 behavioral models,

NOTE Confidence: 0.767347726363636

00:38:05.420 --> 00:38:05.708 right.

NOTE Confidence: 0.767347726363636

00:38:05.708 --> 00:38:08.300 And this is stuff that has to do with

NOTE Confidence: 0.767347726363636

00:38:08.367 --> 00:38:10.251 trustworthiness of the reproducibility

NOTE Confidence: 0.767347726363636

00:38:10.251 --> 00:38:13.540 of those models at the behavioral level.

NOTE Confidence: 0.767347726363636

00:38:13.540 --> 00:38:14.605 No imaging yet.

NOTE Confidence: 0.767347726363636

00:38:14.605 --> 00:38:17.090 This is this is something that that

NOTE Confidence: 0.767347726363636

00:38:17.168 --> 00:38:19.674 we also found out is very important.

NOTE Confidence: 0.767347726363636

00:38:19.680 --> 00:38:22.304 Then Criterion 4 is how do we then

00:38:22.304 --> 00:38:25.109 produce a robust and interpretable

00:38:25.109 --> 00:38:27.548 neuroimaging maps that are linkable

00:38:27.548 --> 00:38:29.296 to that behavioral variation?

00:38:29.300 --> 00:38:30.155 And then finally,

00:38:30.155 --> 00:38:31.865 how do we cross validate that

00:38:31.865 --> 00:38:32.800 brain behavioral?

00:38:32.800 --> 00:38:33.046 Right.

00:38:33.046 --> 00:38:35.260 So this is a lot of stuff to cover

00:38:35.320 --> 00:38:36.460 in like 15 minutes.

00:38:36.460 --> 00:38:38.660 So some of the hit on some of the highlights

00:38:38.710 --> 00:38:40.510 and then we'll pause your questions.

00:38:40.510 --> 00:38:41.866 So this is.

00:38:41.866 --> 00:38:42.770 You know,

00:38:42.770 --> 00:38:44.074 a trivial point, right,

00:38:44.074 --> 00:38:45.704 it's just hard to do,

00:38:45.710 --> 00:38:47.290 which is we need informatics

NOTE Confidence: 0.767347726363636

00:38:47.290 --> 00:38:48.238 solutions that scale.

NOTE Confidence: 0.767347726363636

00:38:48.240 --> 00:38:50.288 And Yale is at the forefront of this.

NOTE Confidence: 0.767347726363636

00:38:50.290 --> 00:38:52.138 I think that what we're doing

NOTE Confidence: 0.767347726363636

00:38:52.138 --> 00:38:53.062 in our department,

NOTE Confidence: 0.767347726363636

00:38:53.070 --> 00:38:54.456 I'm tremendously proud of and I

NOTE Confidence: 0.767347726363636

00:38:54.456 --> 00:38:56.133 think some of the work of faculty

NOTE Confidence: 0.767347726363636

00:38:56.133 --> 00:38:57.778 on this call and others like we're

NOTE Confidence: 0.767347726363636

00:38:57.832 --> 00:38:59.530 really pushing the boundary of this.

NOTE Confidence: 0.767347726363636

00:38:59.530 --> 00:39:01.196 This is the point is really things

NOTE Confidence: 0.767347726363636

00:39:01.196 --> 00:39:03.115 have to scale and drop rate if

NOTE Confidence: 0.767347726363636

00:39:03.115 --> 00:39:04.555 we're going to develop precision

NOTE Confidence: 0.767347726363636

00:39:04.555 --> 00:39:05.702 medicine solutions, right.

NOTE Confidence: 0.767347726363636

00:39:05.702 --> 00:39:07.574 So I'll just forward and just

NOTE Confidence: 0.767347726363636

00:39:07.574 --> 00:39:10.182 say a key thing inside this

NOTE Confidence: 0.767347726363636

00:39:10.182 --> 00:39:12.314 architecture is analytic discovering.

00:39:12.320 --> 00:39:12.629 Years.

00:39:12.629 --> 00:39:14.792 And so this is the workflow from

00:39:14.792 --> 00:39:15.410 Lisa's paper,

00:39:15.410 --> 00:39:17.330 just as a shameless plug.

00:39:17.330 --> 00:39:20.120 But the point is that analytics have to be

00:39:20.120 --> 00:39:22.428 organically built into this for the Discovery

00:39:22.428 --> 00:39:24.868 science engine to work where it cannot be.

00:39:24.870 --> 00:39:27.410 Data collection devoid of analytics.

00:39:27.410 --> 00:39:28.550 It's it's it's all,

00:39:28.550 --> 00:39:29.700 it's all combined, right?

00:39:29.700 --> 00:39:32.020 So talk through how we do this with

00:39:32.020 --> 00:39:34.119 a particular analytic framework using

00:39:34.119 --> 00:39:37.130 a data set that's called Beast Snip.

00:39:37.130 --> 00:39:37.994 Our colleague,

00:39:37.994 --> 00:39:40.586 Godfrey Pearlson was one of the

00:39:40.586 --> 00:39:42.508 principal investigators on the original.

NOTE Confidence: 0.767347726363636

00:39:42.510 --> 00:39:44.350 Snip that made it into the public domain,

NOTE Confidence: 0.767347726363636

00:39:44.350 --> 00:39:46.206 and now they're on to be snipped too.

NOTE Confidence: 0.827432568

00:39:46.210 --> 00:39:47.310 I don't even know three,

NOTE Confidence: 0.827432568

00:39:47.310 --> 00:39:49.080 but this is a public domain

NOTE Confidence: 0.827432568

00:39:49.080 --> 00:39:50.809 datasets that made it into NH.

NOTE Confidence: 0.827432568

00:39:50.810 --> 00:39:53.120 We downloaded it out of the National

NOTE Confidence: 0.827432568

00:39:53.120 --> 00:39:56.068 Debt archive and processed it using the

NOTE Confidence: 0.827432568

00:39:56.068 --> 00:39:57.964 human connectome processing pipelines.

NOTE Confidence: 0.827432568

00:39:57.970 --> 00:39:59.602 Like that's as much as I'll

NOTE Confidence: 0.827432568

00:39:59.602 --> 00:40:01.125 say to speed ahead, OK?

NOTE Confidence: 0.827432568

00:40:01.125 --> 00:40:03.735 So I've shown this several times.

NOTE Confidence: 0.827432568

00:40:03.740 --> 00:40:05.636 Maybe some of you have seen these data,

NOTE Confidence: 0.827432568

00:40:05.640 --> 00:40:07.488 but now it's published and I can kind

NOTE Confidence: 0.827432568

00:40:07.488 --> 00:40:09.395 of show you the full gamut of this.

NOTE Confidence: 0.827432568

00:40:09.400 --> 00:40:12.767 So the first question that we asked

NOTE Confidence: 0.827432568

00:40:12.767 --> 00:40:16.041 ourselves was what is the covariance

NOTE Confidence: 0.827432568

00:40:16.041 --> 00:40:19.515 structure across people in the symptom

NOTE Confidence: 0.827432568

00:40:19.515 --> 00:40:22.480 geometry of the psychosis spectrum

NOTE Confidence: 0.827432568

00:40:22.480 --> 00:40:24.890 population of these 436 people?

NOTE Confidence: 0.827432568

00:40:24.890 --> 00:40:26.615 And you're looking at pans,

NOTE Confidence: 0.827432568

00:40:26.620 --> 00:40:28.480 these are pans items, right?

NOTE Confidence: 0.827432568

00:40:28.480 --> 00:40:31.036 The backs is on top backs,

NOTE Confidence: 0.827432568

00:40:31.040 --> 00:40:32.444 which is the brief.

NOTE Confidence: 0.827432568

00:40:32.444 --> 00:40:33.848 Assessment of cognition and

NOTE Confidence: 0.827432568

00:40:33.848 --> 00:40:35.299 then pans items here.

NOTE Confidence: 0.827432568

00:40:35.300 --> 00:40:37.922 So this is the covariance matrix

NOTE Confidence: 0.827432568

00:40:37.922 --> 00:40:40.212 and there's some correlation between

NOTE Confidence: 0.827432568

00:40:40.212 --> 00:40:41.960 these right across 436 people.

NOTE Confidence: 0.827432568

00:40:41.960 --> 00:40:42.660 So in other words,

NOTE Confidence: 0.827432568

00:40:42.660 --> 00:40:45.030 they're structure between these symptoms,

NOTE Confidence: 0.827432568

00:40:45.030 --> 00:40:46.101 which is expected.

NOTE Confidence: 0.827432568

00:40:46.101 --> 00:40:49.270 This is not new, this is, this makes sense.

NOTE Confidence: 0.827432568

00:40:49.270 --> 00:40:50.745 But when you plotted across

NOTE Confidence: 0.827432568

00:40:50.745 --> 00:40:51.981 the DSM categories, right,

NOTE Confidence: 0.827432568

00:40:51.981 --> 00:40:54.087 where bipolar is shown in yellow,

NOTE Confidence: 0.827432568

00:40:54.090 --> 00:40:55.563 schizoaffective in this

NOTE Confidence: 0.827432568

00:40:55.563 --> 00:40:57.527 kind of orangish color,

NOTE Confidence: 0.827432568

00:40:57.530 --> 00:41:00.026 dark red is schizophrenia and all pro bands,

NOTE Confidence: 0.827432568

00:41:00.030 --> 00:41:01.848 all patients are shown in black,

NOTE Confidence: 0.827432568

00:41:01.850 --> 00:41:05.710 you know, I like to argue that.

NOTE Confidence: 0.827432568

00:41:05.710 --> 00:41:08.868 There's a lot of variation in each one of

NOTE Confidence: 0.827432568

00:41:08.868 --> 00:41:11.900 these sub scores on the pans and cognition,

NOTE Confidence: 0.827432568

00:41:11.900 --> 00:41:13.468 but not really clear,

NOTE Confidence: 0.827432568

00:41:13.468 --> 00:41:15.036 very clear distinctions between

NOTE Confidence: 0.827432568

00:41:15.036 --> 00:41:16.202 diagnostic categories, right?

NOTE Confidence: 0.827432568

00:41:16.202 --> 00:41:18.494 And so this is not news.

NOTE Confidence: 0.827432568

00:41:18.500 --> 00:41:20.420 Psychosis spectrum disorder is heterogeneous,

NOTE Confidence: 0.827432568

00:41:20.420 --> 00:41:21.599 exhibits covariation symptoms

NOTE Confidence: 0.827432568

00:41:21.599 --> 00:41:23.608 across clinical scales. OK, great.

NOTE Confidence: 0.827432568

00:41:23.608 --> 00:41:25.678 You know, cool story Allen.

NOTE Confidence: 0.827432568

00:41:25.680 --> 00:41:26.418 So now what?

NOTE Confidence: 0.827432568

00:41:26.418 --> 00:41:28.140 So the question is what is the

NOTE Confidence: 0.827432568

00:41:28.204 --> 00:41:30.040 dimensionality of this solution,

NOTE Confidence: 0.827432568

00:41:30.040 --> 00:41:30.305 right.

NOTE Confidence: 0.827432568

00:41:30.305 --> 00:41:32.160 Is there a low dimensional solution that

NOTE Confidence: 0.827432568

00:41:32.160 --> 00:41:34.420 we can reduce the map to the brain right.

NOTE Confidence: 0.827432568

00:41:34.420 --> 00:41:37.220 Can we do that and simply right.

NOTE Confidence: 0.827432568

00:41:37.220 --> 00:41:40.006 You could ask is there say principal

NOTE Confidence: 0.827432568

00:41:40.006 --> 00:41:41.620 component analytic solution that

NOTE Confidence: 0.827432568

00:41:41.620 --> 00:41:44.098 explains these data or a factor analytic

NOTE Confidence: 0.827432568

00:41:44.098 --> 00:41:46.617 solution or K means clustering solution,

NOTE Confidence: 0.827432568

00:41:46.620 --> 00:41:48.960 just something that is looking at

NOTE Confidence: 0.827432568

00:41:48.960 --> 00:41:50.935 the covariance structure of the

NOTE Confidence: 0.827432568

00:41:50.935 --> 00:41:53.017 data in a lower dimensional space.

NOTE Confidence: 0.827432568

00:41:53.020 --> 00:41:54.556 And so it turns out yes.

NOTE Confidence: 0.827432568

00:41:54.560 --> 00:41:54.815 Right.

NOTE Confidence: 0.827432568

00:41:54.815 --> 00:41:56.855 So these are the components that come out,

NOTE Confidence: 0.827432568

00:41:56.860 --> 00:41:59.216 which brings me to criterion too, right?

NOTE Confidence: 0.827432568

00:41:59.216 --> 00:42:00.872 Can we select the right measures

NOTE Confidence: 0.827432568

00:42:00.872 --> 00:42:02.706 to map onto the brain? Right.

NOTE Confidence: 0.827432568

00:42:02.706 --> 00:42:05.142 And can we obtain an interpretable

NOTE Confidence: 0.827432568

00:42:05.142 --> 00:42:05.954 solution here?

NOTE Confidence: 0.827432568

00:42:05.960 --> 00:42:06.181 Right.

NOTE Confidence: 0.827432568

00:42:06.181 --> 00:42:07.949 So, I mean, I'm not going to walk

NOTE Confidence: 0.827432568

00:42:07.949 --> 00:42:09.459 through these principal components.

NOTE Confidence: 0.827432568

00:42:09.460 --> 00:42:09.976 More importantly,

NOTE Confidence: 0.827432568

00:42:09.976 --> 00:42:12.341 when I want to highlight is what the geometry

NOTE Confidence: 0.827432568

00:42:12.341 --> 00:42:14.618 looks like just so you can get an intuition.

NOTE Confidence: 0.827432568

00:42:14.620 --> 00:42:16.120 Every dot is a patient.

NOTE Confidence: 0.827432568

00:42:16.120 --> 00:42:18.480 They're color-coded as noted here,

NOTE Confidence: 0.827432568

00:42:18.480 --> 00:42:19.040 right?

NOTE Confidence: 0.827432568

00:42:19.040 --> 00:42:22.400 These arrows in this space are

NOTE Confidence: 0.827432568

00:42:22.400 --> 00:42:25.810 vectors of the pans and backs.

NOTE Confidence: 0.801581658571428

00:42:28.300 --> 00:42:31.877 Average scores. The green arrow is backs,

NOTE Confidence: 0.801581658571428

00:42:31.880 --> 00:42:33.348 which is almost perfectly

NOTE Confidence: 0.801581658571428

00:42:33.348 --> 00:42:35.140 collinear with the cognition axis.

NOTE Confidence: 0.801581658571428

00:42:35.140 --> 00:42:37.060 That's one of the principal components,

NOTE Confidence: 0.801581658571428

00:42:37.060 --> 00:42:39.713 the black dots that you may see

NOTE Confidence: 0.801581658571428

00:42:39.713 --> 00:42:41.360 here healthy controls right?

NOTE Confidence: 0.801581658571428

00:42:41.360 --> 00:42:44.853 And then the two the the the

NOTE Confidence: 0.801581658571428

00:42:44.853 --> 00:42:48.026 arrows that are coming up the

NOTE Confidence: 0.801581658571428

00:42:48.026 --> 00:42:51.673 the blue and the purple are the.

NOTE Confidence: 0.801581658571428

00:42:51.680 --> 00:42:53.952 Negative and positive symptoms,

NOTE Confidence: 0.801581658571428

00:42:53.952 --> 00:42:55.090 respectively, right?

NOTE Confidence: 0.801581658571428

00:42:55.090 --> 00:42:57.940 Notice that they project onto

NOTE Confidence: 0.801581658571428

00:42:57.940 --> 00:43:00.920 this access under an angle.

NOTE Confidence: 0.801581658571428

00:43:00.920 --> 00:43:03.400 It's not. They're not collinear,

NOTE Confidence: 0.801581658571428

00:43:03.400 --> 00:43:06.390 and they're obliquely rotated, right?

NOTE Confidence: 0.801581658571428

00:43:06.390 --> 00:43:08.514 And then there's a global dysfunction

NOTE Confidence: 0.801581658571428

00:43:08.514 --> 00:43:11.153 which is all the patients are not

NOTE Confidence: 0.801581658571428

00:43:11.153 --> 00:43:12.968 functioning as well as controls.

NOTE Confidence: 0.801581658571428

00:43:12.970 --> 00:43:15.070 So it's this PC three that we're

NOTE Confidence: 0.801581658571428

00:43:15.070 --> 00:43:16.792 going to talk about, right.

NOTE Confidence: 0.801581658571428

00:43:16.792 --> 00:43:20.050 So this is a static picture of that solution,

NOTE Confidence: 0.801581658571428

00:43:20.050 --> 00:43:20.513 right.

NOTE Confidence: 0.801581658571428

00:43:20.513 --> 00:43:24.217 And if if you can see after correct

NOTE Confidence: 0.801581658571428

00:43:24.217 --> 00:43:25.880 schizoaffective is misspelled,

NOTE Confidence: 0.801581658571428

00:43:25.880 --> 00:43:27.721 but if you can see the positive

NOTE Confidence: 0.801581658571428

00:43:27.721 --> 00:43:29.010 and the negative vectors,

NOTE Confidence: 0.801581658571428

00:43:29.010 --> 00:43:32.270 they form a 45 degree angle onto PC-3.

NOTE Confidence: 0.801581658571428

00:43:32.270 --> 00:43:32.550 OK.

NOTE Confidence: 0.801581658571428

00:43:32.550 --> 00:43:34.510 So now what is this action you

NOTE Confidence: 0.801581658571428

00:43:34.510 --> 00:43:36.289 look like numerically, right?

NOTE Confidence: 0.801581658571428

00:43:36.289 --> 00:43:39.321 Zoom in and these are the linear combinations

NOTE Confidence: 0.801581658571428

00:43:39.321 --> 00:43:42.140 and this solution right in this sample.

NOTE Confidence: 0.801581658571428

00:43:42.140 --> 00:43:44.177 So if I plot the DSM categories,

NOTE Confidence: 0.801581658571428

00:43:44.180 --> 00:43:46.620 you'd say there's an effect.

NOTE Confidence: 0.801581658571428

00:43:46.620 --> 00:43:48.500 Right. They don't differ,

NOTE Confidence: 0.801581658571428

00:43:48.500 --> 00:43:50.850 but that's actually the point.

NOTE Confidence: 0.801581658571428

00:43:50.850 --> 00:43:53.853 The point is that when you cut

NOTE Confidence: 0.801581658571428

00:43:53.853 --> 00:43:55.969 through this geometry with the.

NOTE Confidence: 0.801581658571428

00:43:55.970 --> 00:43:56.616 Data-driven solution.

NOTE Confidence: 0.801581658571428

00:43:56.616 --> 00:43:59.200 You ought not to see differences in DSM

NOTE Confidence: 0.801581658571428

00:43:59.255 --> 00:44:01.541 categories because they don't seem to

NOTE Confidence: 0.801581658571428

00:44:01.541 --> 00:44:03.318 actually follow natural variation, right?

NOTE Confidence: 0.801581658571428

00:44:03.318 --> 00:44:05.967 And so how can I convince you of that, right?

NOTE Confidence: 0.801581658571428

00:44:05.967 --> 00:44:06.384 So.

NOTE Confidence: 0.801581658571428

00:44:06.384 --> 00:44:09.303 So let's take a look at the

NOTE Confidence: 0.801581658571428

00:44:09.303 --> 00:44:11.508 configuration of the PC-3 items, right.

NOTE Confidence: 0.801581658571428

00:44:11.508 --> 00:44:13.944 So typical person would be somewhat

NOTE Confidence: 0.801581658571428

00:44:13.950 --> 00:44:15.660 delusional, conceptual, disorganized.

NOTE Confidence: 0.801581658571428

00:44:15.660 --> 00:44:17.370 They are hallucinating,

NOTE Confidence: 0.801581658571428

00:44:17.370 --> 00:44:18.882 they have some excitement,

NOTE Confidence: 0.801581658571428

00:44:18.882 --> 00:44:19.711 grandiosity, right?

NOTE Confidence: 0.801581658571428

00:44:19.711 --> 00:44:21.966 But they're not, you know,

NOTE Confidence: 0.801581658571428

00:44:21.970 --> 00:44:23.848 purely collinear with the negative symptoms.

NOTE Confidence: 0.801581658571428

00:44:23.850 --> 00:44:25.548 They have something, some they don't.

NOTE Confidence: 0.801581658571428

00:44:25.550 --> 00:44:27.158 They're a little bit cognitively impaired,

NOTE Confidence: 0.801581658571428

00:44:27.160 --> 00:44:27.633 right?

00:44:27.633 --> 00:44:30.668 But again not a clean, you know,

00:44:30.668 --> 00:44:33.340 one to one mapping between these these axes,

00:44:33.340 --> 00:44:35.700 right, between the the subscores of the pans.

00:44:35.700 --> 00:44:36.540 So again, you know,

00:44:36.540 --> 00:44:37.800 let's put this to the test

00:44:37.847 --> 00:44:39.077 I I'm a competitive person,

00:44:39.080 --> 00:44:40.448 I like competition, right.

00:44:40.448 --> 00:44:43.060 And and I like to, you know,

00:44:43.060 --> 00:44:43.960 create competitions,

00:44:43.960 --> 00:44:45.155 incentive questions, right.

00:44:45.155 --> 00:44:47.515 So let's see is the SM going to

00:44:47.515 --> 00:44:49.643 outperform a data-driven solution, right.

00:44:49.643 --> 00:44:52.324 Because we need it to map it

00:44:52.324 --> 00:44:53.417 onto pharmacology, right?

00:44:53.417 --> 00:44:57.790 Like we need something that is robust, so.

00:44:57.790 --> 00:44:58.534 Criterion 3.

NOTE Confidence: 0.801581658571428

00:44:58.534 --> 00:45:00.766 Before we even get there right,

NOTE Confidence: 0.801581658571428

00:45:00.770 --> 00:45:02.642 we have to check that the

NOTE Confidence: 0.801581658571428

00:45:02.642 --> 00:45:04.609 solution of this model is stable.

NOTE Confidence: 0.801581658571428

00:45:04.610 --> 00:45:07.202 So this is a summary of the leave

NOTE Confidence: 0.801581658571428

00:45:07.202 --> 00:45:09.508 each site out cross validation,

NOTE Confidence: 0.801581658571428

00:45:09.510 --> 00:45:11.160 a summary of the predicted

NOTE Confidence: 0.801581658571428

00:45:11.160 --> 00:45:12.150 versus observed scores,

NOTE Confidence: 0.801581658571428

00:45:12.150 --> 00:45:14.550 a summary of the predicted versus

NOTE Confidence: 0.801581658571428

00:45:14.550 --> 00:45:16.150 observed single subject scores

NOTE Confidence: 0.801581658571428

00:45:16.221 --> 00:45:17.849 from K fold bootstrapping,

NOTE Confidence: 0.801581658571428

00:45:17.850 --> 00:45:19.908 and similarity of the actual loadings

NOTE Confidence: 0.801581658571428

00:45:19.908 --> 00:45:22.927 on the PCA for leave site out five

NOTE Confidence: 0.801581658571428

00:45:22.927 --> 00:45:24.902 fold bootstrapping and split half.

NOTE Confidence: 0.801581658571428

00:45:24.910 --> 00:45:26.512 And hopefully this shows you that

NOTE Confidence: 0.801581658571428

00:45:26.512 --> 00:45:27.970 the solution is really stable.

NOTE Confidence: 0.801581658571428

00:45:27.970 --> 00:45:29.770 Which means that the basement consortium

NOTE Confidence: 0.801581658571428

00:45:29.770 --> 00:45:31.699 did a really good job actually,

NOTE Confidence: 0.801581658571428

00:45:31.700 --> 00:45:32.088 right.

NOTE Confidence: 0.801581658571428

00:45:32.088 --> 00:45:34.416 They collected and and asset clinically

NOTE Confidence: 0.801581658571428

00:45:34.416 --> 00:45:36.854 the data in a very consistent way

NOTE Confidence: 0.801581658571428

00:45:36.854 --> 00:45:39.212 and we're able to get a pretty

NOTE Confidence: 0.801581658571428

00:45:39.212 --> 00:45:41.140 good stable behavioral model,

NOTE Confidence: 0.715133701428571

00:45:41.140 --> 00:45:44.654 right. So the PCA variance is generalizes,

NOTE Confidence: 0.715133701428571

00:45:44.660 --> 00:45:46.496 the score is generalized and the

NOTE Confidence: 0.715133701428571

00:45:46.496 --> 00:45:47.683 PC weights generalized, right.

NOTE Confidence: 0.715133701428571

00:45:47.683 --> 00:45:49.524 Otherwise why are we mapping it onto

NOTE Confidence: 0.715133701428571

00:45:49.524 --> 00:45:51.596 the brain if it doesn't, right? Cool.

NOTE Confidence: 0.715133701428571

00:45:51.596 --> 00:45:54.382 So now let's actually go even further

NOTE Confidence: 0.715133701428571

00:45:54.382 --> 00:45:57.470 from DSM and take pans positive symptoms.

NOTE Confidence: 0.715133701428571

00:45:57.470 --> 00:45:59.304 Let's give pans a fair shot because

NOTE Confidence: 0.715133701428571

00:45:59.304 --> 00:46:01.464 this is what the industry uses, right?

NOTE Confidence: 0.715133701428571

00:46:01.464 --> 00:46:03.468 If you're going to test if

NOTE Confidence: 0.715133701428571

00:46:03.468 --> 00:46:04.470 a antipsychotic works,

NOTE Confidence: 0.715133701428571

00:46:04.470 --> 00:46:06.227 you're going to use pans positive symptoms.

NOTE Confidence: 0.715133701428571

00:46:06.230 --> 00:46:07.208 That's your benchmark.

NOTE Confidence: 0.715133701428571

00:46:07.208 --> 00:46:09.490 That's the gold standard for the industry,

NOTE Confidence: 0.715133701428571

00:46:09.490 --> 00:46:12.754 right. And and this is the

NOTE Confidence: 0.715133701428571

00:46:12.754 --> 00:46:14.930 psychosis configuration PCA effect,

NOTE Confidence: 0.715133701428571

00:46:14.930 --> 00:46:18.002 which required only only one level

NOTE Confidence: 0.715133701428571

00:46:18.002 --> 00:46:20.550 of supervision, which is to pick PCA.

NOTE Confidence: 0.715133701428571

00:46:20.550 --> 00:46:21.750 That's it. We just said.

NOTE Confidence: 0.715133701428571

00:46:21.750 --> 00:46:23.102 Let's run a PCA.

NOTE Confidence: 0.715133701428571

00:46:23.102 --> 00:46:24.800 So now, which one will give you

NOTE Confidence: 0.715133701428571

00:46:24.800 --> 00:46:25.933 a better brain map, right?

NOTE Confidence: 0.715133701428571

00:46:25.933 --> 00:46:27.498 That's what we care about.

NOTE Confidence: 0.715133701428571

00:46:27.500 --> 00:46:30.559 We care which Brain Mac is better.

NOTE Confidence: 0.715133701428571

00:46:30.560 --> 00:46:31.355 And so again,

NOTE Confidence: 0.715133701428571

00:46:31.355 --> 00:46:33.210 we're going to use GBC as the

NOTE Confidence: 0.715133701428571

00:46:33.271 --> 00:46:35.521 brain measure and we're going to

NOTE Confidence: 0.715133701428571

00:46:35.521 --> 00:46:37.400 calculate the variation from each.

NOTE Confidence: 0.715133701428571

00:46:37.400 --> 00:46:39.647 Parcel to every other parcel using this

NOTE Confidence: 0.715133701428571

00:46:39.647 --> 00:46:41.240 quantitative technique that I explained,

NOTE Confidence: 0.715133701428571

00:46:41.240 --> 00:46:41.597 right.

NOTE Confidence: 0.715133701428571

00:46:41.597 --> 00:46:44.453 And so the intuition again is that we're

NOTE Confidence: 0.715133701428571

00:46:44.453 --> 00:46:47.246 going to get this value for every parcel.

NOTE Confidence: 0.715133701428571

00:46:47.250 --> 00:46:49.395 We're going to then correlate

NOTE Confidence: 0.715133701428571

00:46:49.395 --> 00:46:52.080 the area level signal with the

NOTE Confidence: 0.715133701428571

00:46:52.080 --> 00:46:53.920 symptom for every patient.

NOTE Confidence: 0.715133701428571

00:46:53.920 --> 00:46:56.192 And then we're going to get in a

NOTE Confidence: 0.715133701428571

00:46:56.192 --> 00:46:58.079 cross subject map that tells us

NOTE Confidence: 0.715133701428571

00:46:58.079 --> 00:46:59.963 how people vary across the sample

NOTE Confidence: 0.715133701428571

00:47:00.034 --> 00:47:01.962 with respect to their GBC, right.

00:47:01.962 --> 00:47:03.894 So it's an individual difference analysis.

00:47:03.900 --> 00:47:07.020 And so this is the map you get with pans

00:47:07.107 --> 00:47:08.659 with 436 people and this is the map.

00:47:08.660 --> 00:47:12.001 You get when you use the PC-3.

00:47:12.001 --> 00:47:12.402 Now.

00:47:12.402 --> 00:47:15.209 I want to just pause here because

00:47:15.209 --> 00:47:16.965 hopefully it's self-evident to

00:47:16.965 --> 00:47:19.085 everybody which one is better

00:47:19.085 --> 00:47:21.200 and if somebody says a.

00:47:21.200 --> 00:47:23.510 I I hope they're joking.

00:47:23.510 --> 00:47:23.971 So.

00:47:23.971 --> 00:47:27.198 This is not nothing done except simply

00:47:27.198 --> 00:47:29.507 taking a data-driven behavioral

00:47:29.507 --> 00:47:32.737 analysis of pens and backs,

00:47:32.740 --> 00:47:34.950 a data-driven neural measure with

NOTE Confidence: 0.715133701428571

00:47:34.950 --> 00:47:37.660 the only piece of supervision being.

NOTE Confidence: 0.715133701428571

00:47:37.660 --> 00:47:41.307 Reduction of the FC matrix using GBC.

NOTE Confidence: 0.715133701428571

00:47:41.310 --> 00:47:43.417 And then you get this slice through

NOTE Confidence: 0.715133701428571

00:47:43.417 --> 00:47:45.064 the geometry that hopefully one

NOTE Confidence: 0.715133701428571

00:47:45.064 --> 00:47:47.110 could argue is is better and

NOTE Confidence: 0.715133701428571

00:47:47.110 --> 00:47:48.792 quantitatively it is better, right?

NOTE Confidence: 0.715133701428571

00:47:48.792 --> 00:47:51.024 You can actually check that statistically

NOTE Confidence: 0.715133701428571

00:47:51.024 --> 00:47:52.965 that the variance covered is higher

NOTE Confidence: 0.715133701428571

00:47:52.965 --> 00:47:55.760 and that the range of the Z values is better.

NOTE Confidence: 0.715133701428571

00:47:55.760 --> 00:47:57.064 You can do all sorts of other things,

NOTE Confidence: 0.715133701428571

00:47:57.070 --> 00:47:59.150 but it's just better.

NOTE Confidence: 0.715133701428571

00:47:59.150 --> 00:48:03.042 So, OK, now we have something right

NOTE Confidence: 0.715133701428571

00:48:03.042 --> 00:48:05.290 now criterion 5 is,

NOTE Confidence: 0.715133701428571

00:48:05.290 --> 00:48:07.014 is this thing generalizable?

NOTE Confidence: 0.715133701428571

00:48:07.014 --> 00:48:11.009 And what I mean by that is if I were to.

NOTE Confidence: 0.715133701428571

00:48:11.010 --> 00:48:12.650 Say Mark or Chris,

NOTE Confidence: 0.715133701428571

00:48:12.650 --> 00:48:15.110 can you guys use the weights,

NOTE Confidence: 0.715133701428571

00:48:15.110 --> 00:48:17.528 the actual thing that I found

NOTE Confidence: 0.715133701428571

00:48:17.530 --> 00:48:21.418 here and reproduce the exact map?

NOTE Confidence: 0.715133701428571

00:48:21.420 --> 00:48:23.844 Using a split half cross validation

NOTE Confidence: 0.715133701428571

00:48:23.844 --> 00:48:25.056 of the model,

NOTE Confidence: 0.715133701428571

00:48:25.060 --> 00:48:27.937 can you get the same picture again?

NOTE Confidence: 0.715133701428571

00:48:27.940 --> 00:48:29.398 That's that's what we care about.

NOTE Confidence: 0.715133701428571

00:48:29.400 --> 00:48:31.016 Not just that you can point to five,

NOTE Confidence: 0.715133701428571

00:48:31.020 --> 00:48:32.940 reject the null and publish,

NOTE Confidence: 0.715133701428571

00:48:32.940 --> 00:48:35.964 but that the picture of the neural

NOTE Confidence: 0.715133701428571

00:48:35.964 --> 00:48:37.260 topography is reproducible.

NOTE Confidence: 0.715133701428571

00:48:37.260 --> 00:48:39.258 And this is what we get in this case,

NOTE Confidence: 0.715133701428571

00:48:39.260 --> 00:48:39.683 right?

NOTE Confidence: 0.715133701428571

00:48:39.683 --> 00:48:42.652 So and we did this 10,000 times,

NOTE Confidence: 0.715133701428571

00:48:42.652 --> 00:48:46.060 but half and various ways and tried to

NOTE Confidence: 0.854820509166667

00:48:46.143 --> 00:48:48.448 break it. You know, pretty robust.

NOTE Confidence: 0.854820509166667

00:48:48.448 --> 00:48:51.588 Both dense level and the parcel level, right?

NOTE Confidence: 0.854820509166667

00:48:51.588 --> 00:48:53.901 And this is only 219 people, right?

NOTE Confidence: 0.854820509166667

00:48:53.901 --> 00:48:56.223 We're not talking gargantuan samples here,

NOTE Confidence: 0.854820509166667

00:48:56.230 --> 00:48:59.472 right? It's just that you have the

NOTE Confidence: 0.854820509166667

00:48:59.472 --> 00:49:01.220 right slice through the geometry and

NOTE Confidence: 0.854820509166667

00:49:01.220 --> 00:49:03.236 then all of a sudden you're getting

NOTE Confidence: 0.854820509166667

00:49:03.236 --> 00:49:05.326 maps that reproduce even in patients.

NOTE Confidence: 0.854820509166667

00:49:05.330 --> 00:49:08.130 So now this is the engine that we

NOTE Confidence: 0.854820509166667

00:49:08.130 --> 00:49:10.941 submit this to in order to select

NOTE Confidence: 0.854820509166667

00:49:10.941 --> 00:49:12.823 the most stable features, right.

NOTE Confidence: 0.854820509166667

00:49:12.823 --> 00:49:14.594 And I'm not going to walk through

NOTE Confidence: 0.854820509166667

00:49:14.594 --> 00:49:16.150 this because it's certainly dense,

NOTE Confidence: 0.854820509166667

00:49:16.150 --> 00:49:18.706 but it's, it's simply, you know,

NOTE Confidence: 0.854820509166667

00:49:18.710 --> 00:49:21.170 under the hood it's some basic

NOTE Confidence: 0.854820509166667

00:49:21.170 --> 00:49:23.292 linear algebra of optimizing each

NOTE Confidence: 0.854820509166667

00:49:23.292 --> 00:49:25.342 feature in relation to stability

NOTE Confidence: 0.854820509166667

00:49:25.342 --> 00:49:27.749 criteria from the out of sample.

NOTE Confidence: 0.854820509166667

00:49:27.750 --> 00:49:28.114 Generalization.

NOTE Confidence: 0.854820509166667

00:49:28.114 --> 00:49:31.795 And so then you can ask the question of which

NOTE Confidence: 0.854820509166667

00:49:31.795 --> 00:49:34.774 parcels of the map should we trust the most?

NOTE Confidence: 0.854820509166667

00:49:34.780 --> 00:49:36.220 And those are the parcels that

NOTE Confidence: 0.854820509166667

00:49:36.220 --> 00:49:38.326 then we can use as a, you know,

NOTE Confidence: 0.854820509166667

00:49:38.326 --> 00:49:39.978 for further feature engineering.

NOTE Confidence: 0.854820509166667

00:49:39.980 --> 00:49:40.546 Interestingly though,

NOTE Confidence: 0.854820509166667

00:49:40.546 --> 00:49:42.810 what you can also do is then once

NOTE Confidence: 0.854820509166667

00:49:42.871 --> 00:49:44.755 you've done this and you find

NOTE Confidence: 0.854820509166667

00:49:44.755 --> 00:49:46.011 your trustworthy parcels right,

NOTE Confidence: 0.854820509166667

00:49:46.020 --> 00:49:48.220 the ones that truly generalize,

NOTE Confidence: 0.854820509166667

00:49:48.220 --> 00:49:50.938 you can then ask how do they covary in

NOTE Confidence: 0.854820509166667

00:49:50.938 --> 00:49:53.626 relation to the behavioral feature selection?

NOTE Confidence: 0.854820509166667

00:49:53.630 --> 00:49:55.610 Turns out there's a nonlinear relationship,

NOTE Confidence: 0.854820509166667

00:49:55.610 --> 00:49:55.933 right?

NOTE Confidence: 0.854820509166667

00:49:55.933 --> 00:49:58.194 Which means that the more extreme the

NOTE Confidence: 0.854820509166667

00:49:58.194 --> 00:50:00.579 person is on their behavioral loading,

NOTE Confidence: 0.854820509166667

00:50:00.580 --> 00:50:03.247 the more you trust their neural net.

NOTE Confidence: 0.854820509166667

00:50:03.250 --> 00:50:05.022 That makes sense, right?

NOTE Confidence: 0.854820509166667

00:50:05.022 --> 00:50:05.908 That's intuitive.

NOTE Confidence: 0.854820509166667

00:50:05.910 --> 00:50:08.952 And so when you then do this and purely

NOTE Confidence: 0.854820509166667

00:50:08.952 --> 00:50:11.210 filter people based on behavior,

NOTE Confidence: 0.854820509166667

00:50:11.210 --> 00:50:12.938 just take the 10th.

NOTE Confidence: 0.854820509166667

00:50:12.938 --> 00:50:15.530 And the 90th percentiles of the

NOTE Confidence: 0.854820509166667

00:50:15.616 --> 00:50:18.916 behavioral scores and segment that way.

NOTE Confidence: 0.854820509166667

00:50:18.920 --> 00:50:22.280 Then you can begin to segment

NOTE Confidence: 0.854820509166667

00:50:22.280 --> 00:50:24.520 based on neurobehavioral similarity

NOTE Confidence: 0.854820509166667

00:50:24.606 --> 00:50:26.760 of the map until you get.

NOTE Confidence: 0.854820509166667

00:50:26.760 --> 00:50:28.874 To the very peak of this patient

NOTE Confidence: 0.854820509166667

00:50:28.874 --> 00:50:30.958 selection and then you ask how accurate

NOTE Confidence: 0.854820509166667

00:50:30.958 --> 00:50:33.600 is this model and then you can see that

NOTE Confidence: 0.854820509166667

00:50:33.600 --> 00:50:35.714 it's pretty damn accurate at a sample,

NOTE Confidence: 0.854820509166667

00:50:35.720 --> 00:50:36.007 right.

NOTE Confidence: 0.854820509166667

00:50:36.007 --> 00:50:38.303 So in other words it's classifying people as

NOTE Confidence: 0.854820509166667

00:50:38.303 --> 00:50:40.539 plus or minus and in terms of their range.

NOTE Confidence: 0.854820509166667

00:50:40.540 --> 00:50:42.990 And then you can repeat this on

NOTE Confidence: 0.854820509166667

00:50:42.990 --> 00:50:44.428 a completely independent sample

NOTE Confidence: 0.854820509166667

00:50:44.428 --> 00:50:46.354 and again show that it works.

NOTE Confidence: 0.854820509166667

00:50:46.360 --> 00:50:48.278 In terms of segmentation by the way,

NOTE Confidence: 0.854820509166667

00:50:48.280 --> 00:50:48.848 Chris,

NOTE Confidence: 0.854820509166667

00:50:48.848 --> 00:50:53.392 this is the OCD and and skids data

NOTE Confidence: 0.854820509166667

00:50:53.392 --> 00:50:55.485 set which is cross diagnostic that

NOTE Confidence: 0.854820509166667

00:50:55.485 --> 00:50:57.234 we tried this with, right so.

NOTE Confidence: 0.854820509166667

00:50:57.234 --> 00:50:58.544 This isn't even patients schizophrenia

NOTE Confidence: 0.854820509166667

00:50:58.544 --> 00:50:59.068 anymore right.

NOTE Confidence: 0.854820509166667

00:50:59.070 --> 00:51:01.338 It's just saying does your brain

NOTE Confidence: 0.854820509166667

00:51:01.338 --> 00:51:04.266 map look like some norm that we

NOTE Confidence: 0.854820509166667

00:51:04.266 --> 00:51:06.046 can behaviorally incur right.

NOTE Confidence: 0.854820509166667

00:51:06.050 --> 00:51:08.135 So it's really about symptom

NOTE Confidence: 0.854820509166667

00:51:08.135 --> 00:51:08.969 configurations right.

NOTE Confidence: 0.854820509166667

00:51:08.970 --> 00:51:11.226 No longer about our you know,

NOTE Confidence: 0.854820509166667

00:51:11.230 --> 00:51:12.982 do you have a diagnostic category

NOTE Confidence: 0.854820509166667

00:51:12.982 --> 00:51:13.904 in it anyway,

NOTE Confidence: 0.854820509166667

00:51:13.904 --> 00:51:15.908 how can we leverage gene expression

NOTE Confidence: 0.854820509166667

00:51:15.908 --> 00:51:17.610 out to molecularly benchmark this

NOTE Confidence: 0.854820509166667

00:51:17.610 --> 00:51:19.548 and link it back to pharmacology.

NOTE Confidence: 0.854820509166667

00:51:19.550 --> 00:51:21.374 So again I'm going to just remind you

NOTE Confidence: 0.854820509166667

00:51:21.374 --> 00:51:23.304 of this framework Gemini dot, right.

NOTE Confidence: 0.854820509166667

00:51:23.304 --> 00:51:26.136 So now we can take this PC three

NOTE Confidence: 0.854820509166667

00:51:26.136 --> 00:51:28.220 map that is trustworthy.

NOTE Confidence: 0.854820509166667

00:51:28.220 --> 00:51:28.920 And again,

NOTE Confidence: 0.854820509166667

00:51:28.920 --> 00:51:30.670 correlated with gene expression patterns

NOTE Confidence: 0.854820509166667

00:51:30.670 --> 00:51:33.399 in the same way that we've done with MSD.

NOTE Confidence: 0.854820509166667

00:51:33.400 --> 00:51:35.017 And this is just proof of principle,

NOTE Confidence: 0.854820509166667

00:51:35.020 --> 00:51:35.342 right?

NOTE Confidence: 0.854820509166667

00:51:35.342 --> 00:51:37.274 Again, we can show some relationships,

NOTE Confidence: 0.854820509166667

00:51:37.280 --> 00:51:39.179 I'm not going to get into this too much,

NOTE Confidence: 0.854820509166667

00:51:39.180 --> 00:51:40.329 but for instance,

NOTE Confidence: 0.854820509166667

00:51:40.329 --> 00:51:43.010 you can show that the interneuron markers

NOTE Confidence: 0.768201470772727

00:51:43.076 --> 00:51:45.411 or GABA subunits or serotonin

NOTE Confidence: 0.768201470772727

00:51:45.411 --> 00:51:46.812 receptor subunits have

NOTE Confidence: 0.768201470772727

00:51:46.812 --> 00:51:48.400 correspondence with this map.

NOTE Confidence: 0.768201470772727

00:51:48.400 --> 00:51:51.515 It's I'm not claiming mechanism or anything,

NOTE Confidence: 0.768201470772727

00:51:51.520 --> 00:51:52.780 I'm just saying you could do this,

NOTE Confidence: 0.768201470772727

00:51:52.780 --> 00:51:54.920 right. This is doable.

NOTE Confidence: 0.768201470772727

00:51:54.920 --> 00:51:58.866 But finally to conclude, you can then.

NOTE Confidence: 0.768201470772727

00:51:58.866 --> 00:52:01.274 Benchmark this against our

NOTE Confidence: 0.768201470772727

00:52:01.274 --> 00:52:02.478 pharmacological targets.

NOTE Confidence: 0.768201470772727

00:52:02.480 --> 00:52:05.630 So this is actually an in vivo ketamine map,

NOTE Confidence: 0.768201470772727

00:52:05.630 --> 00:52:07.262 same GBC measure,

NOTE Confidence: 0.768201470772727

00:52:07.262 --> 00:52:09.438 healthies versus healthy people,

NOTE Confidence: 0.768201470772727

00:52:09.440 --> 00:52:10.530 placebo versus.

NOTE Confidence: 0.822075590526316

00:52:13.210 --> 00:52:14.048 Infusion, right?

NOTE Confidence: 0.822075590526316

00:52:14.048 --> 00:52:17.400 And then we can select people along the

NOTE Confidence: 0.822075590526316

00:52:17.482 --> 00:52:20.080 axis that presumably varies in relation

NOTE Confidence: 0.822075590526316

00:52:20.080 --> 00:52:22.560 to that work without ever optimizing it.

NOTE Confidence: 0.822075590526316

00:52:22.560 --> 00:52:24.035 We're not optimizing it yet.

NOTE Confidence: 0.822075590526316

00:52:24.040 --> 00:52:25.456 And then you take two people

NOTE Confidence: 0.822075590526316

00:52:25.456 --> 00:52:26.670 on the extreme ends, right,

NOTE Confidence: 0.822075590526316

00:52:26.670 --> 00:52:28.560 and these are their actual brain maps.

NOTE Confidence: 0.822075590526316

00:52:28.560 --> 00:52:29.985 These are two people diagnosed

NOTE Confidence: 0.822075590526316

00:52:29.985 --> 00:52:30.831 with schizophrenia, right?

NOTE Confidence: 0.822075590526316

00:52:30.831 --> 00:52:32.457 They both have the same diagnosis.

NOTE Confidence: 0.822075590526316

00:52:32.460 --> 00:52:34.652 Yet I'd like to argue that their symptom

NOTE Confidence: 0.822075590526316

00:52:34.652 --> 00:52:35.844 configurations are completely different

NOTE Confidence: 0.822075590526316

00:52:35.844 --> 00:52:37.937 and their brains don't look the same.

NOTE Confidence: 0.822075590526316

00:52:37.940 --> 00:52:39.550 Right. Yet we're treating them the same.

NOTE Confidence: 0.822075590526316

00:52:39.550 --> 00:52:42.030 We're giving D2 blockers to both of these

NOTE Confidence: 0.822075590526316

00:52:42.030 --> 00:52:44.430 people as the initial line of defense,

NOTE Confidence: 0.822075590526316

00:52:44.430 --> 00:52:45.870 when in fact, who knows,

NOTE Confidence: 0.822075590526316

00:52:45.870 --> 00:52:46.845 maybe one person would respond

NOTE Confidence: 0.822075590526316

00:52:46.845 --> 00:52:48.070 way better to close the people.

NOTE Confidence: 0.822075590526316

00:52:48.070 --> 00:52:49.799 And we have no idea that that

NOTE Confidence: 0.822075590526316

00:52:49.799 --> 00:52:51.766 is true or not true, right?

NOTE Confidence: 0.822075590526316

00:52:51.766 --> 00:52:56.008 But you can then quantify that using.

NOTE Confidence: 0.822075590526316

00:52:56.010 --> 00:52:56.377 This.

NOTE Confidence: 0.822075590526316

00:52:56.377 --> 00:52:58.579 Framework that Lisa has advanced in

NOTE Confidence: 0.822075590526316

00:52:58.579 --> 00:53:01.383 relation to a given target and you can

NOTE Confidence: 0.822075590526316

00:53:01.383 --> 00:53:03.991 say which person is more similar, right?

NOTE Confidence: 0.822075590526316

00:53:03.991 --> 00:53:06.182 So this person looks like PC-3,

NOTE Confidence: 0.822075590526316

00:53:06.182 --> 00:53:07.510 which looks like ketamine.

NOTE Confidence: 0.822075590526316

00:53:07.510 --> 00:53:09.076 So presumably this person will get

NOTE Confidence: 0.822075590526316

00:53:09.076 --> 00:53:11.338 worse if you give them ketamine and this

NOTE Confidence: 0.822075590526316

00:53:11.338 --> 00:53:13.398 person would maybe even get better, right?

NOTE Confidence: 0.822075590526316

00:53:13.398 --> 00:53:14.322 I don't know.

NOTE Confidence: 0.822075590526316

00:53:14.322 --> 00:53:16.952 But you could do the same thing with

NOTE Confidence: 0.822075590526316

00:53:16.952 --> 00:53:19.437 LSD now and repeat this for another

NOTE Confidence: 0.822075590526316

00:53:19.437 --> 00:53:22.008 access and recapitulate this principle.

NOTE Confidence: 0.822075590526316

00:53:22.010 --> 00:53:26.574 Now these maps can be iteratively optimized.

NOTE Confidence: 0.822075590526316

00:53:26.580 --> 00:53:27.879 This is a.

NOTE Confidence: 0.822075590526316

00:53:27.879 --> 00:53:29.178 Feature selection problem.

NOTE Confidence: 0.822075590526316

00:53:29.180 --> 00:53:31.136 Now we can use the LSD,

NOTE Confidence: 0.822075590526316

00:53:31.140 --> 00:53:32.636 psychedelic or ketamine target

NOTE Confidence: 0.822075590526316

00:53:32.636 --> 00:53:34.880 maps to find people who may

NOTE Confidence: 0.822075590526316

00:53:34.952 --> 00:53:37.020 benefit the most quantitatively,

NOTE Confidence: 0.822075590526316

00:53:37.020 --> 00:53:37.517 rationally,

NOTE Confidence: 0.822075590526316

00:53:37.517 --> 00:53:40.996 iteratively in a fast fail algorithm that

NOTE Confidence: 0.822075590526316

00:53:40.996 --> 00:53:43.555 says these two patient populations ought

NOTE Confidence: 0.822075590526316

00:53:43.555 --> 00:53:46.520 to show the opposite effects of this drug.

NOTE Confidence: 0.822075590526316

00:53:46.520 --> 00:53:48.155 And that's a strong inference

NOTE Confidence: 0.822075590526316

00:53:48.155 --> 00:53:49.335 rational framework, right?

NOTE Confidence: 0.822075590526316

00:53:49.335 --> 00:53:51.960 And so just to summarize,

NOTE Confidence: 0.822075590526316

00:53:51.960 --> 00:53:53.958 like I do think we need

NOTE Confidence: 0.822075590526316

00:53:53.958 --> 00:53:54.957 informatics and scalability.

NOTE Confidence: 0.822075590526316

00:53:54.960 --> 00:53:57.678 I do think we need to first and foremost.

NOTE Confidence: 0.822075590526316

00:53:57.680 --> 00:53:58.492 Their behavior,

NOTE Confidence: 0.822075590526316

00:53:58.492 --> 00:53:58.898 right?

00:53:58.898 --> 00:54:01.740 Select the right combination we need to

00:54:01.812 --> 00:54:03.908 achieve criteria for trustworthiness

00:54:03.908 --> 00:54:06.642 of those behavioral models, right?

00:54:06.642 --> 00:54:09.170 That's that's a must.

00:54:09.170 --> 00:54:11.990 Then and only then do we go to brain imaging,

00:54:11.990 --> 00:54:14.288 and then we need an interpretable.

00:54:14.290 --> 00:54:16.595 Robust and generalizable solution of

00:54:16.595 --> 00:54:20.391 the brain back which in turn then we

00:54:20.391 --> 00:54:22.736 can cross validate with pharmacological

00:54:22.736 --> 00:54:25.907 and gene expression and other metrics

00:54:25.910 --> 00:54:28.350 that that the field is bringing to bear.

00:54:28.350 --> 00:54:29.150 So, so in summary,

00:54:29.150 --> 00:54:31.047 I I do think that we have an

00:54:31.047 --> 00:54:31.921 opportunity here, right.

00:54:31.921 --> 00:54:33.769 I think that what we're doing in our

00:54:33.769 --> 00:54:35.069 department is truly transformative.

NOTE Confidence: 0.822075590526316

00:54:35.070 --> 00:54:37.310 I'm just one out of many people who

NOTE Confidence: 0.822075590526316

00:54:37.310 --> 00:54:39.881 are doing this work and we have I

NOTE Confidence: 0.822075590526316

00:54:39.881 --> 00:54:42.217 think an iterative framework right for

NOTE Confidence: 0.822075590526316

00:54:42.217 --> 00:54:44.169 really dissecting heterogeneity with.

NOTE Confidence: 0.822075590526316

00:54:44.170 --> 00:54:45.250 Imaging and behavior.

NOTE Confidence: 0.822075590526316

00:54:45.250 --> 00:54:47.410 And this can be optimized actually

NOTE Confidence: 0.822075590526316

00:54:47.410 --> 00:54:49.456 again for patient selection and

NOTE Confidence: 0.822075590526316

00:54:49.456 --> 00:54:51.486 precise delivery of of psychedelic

NOTE Confidence: 0.822075590526316

00:54:51.486 --> 00:54:53.179 compounds to the right patient.

NOTE Confidence: 0.822075590526316

00:54:53.180 --> 00:54:54.638 So I'll stop there and think

NOTE Confidence: 0.822075590526316

00:54:54.638 --> 00:54:55.610 I'm actually in time.

NOTE Confidence: 0.822075590526316

00:54:55.610 --> 00:54:56.120 Remarkable.

NOTE Confidence: 0.51398486

00:54:58.180 --> 00:55:01.669 Impressive. Thank you, Alan.

NOTE Confidence: 0.51398486

00:55:01.669 --> 00:55:03.727 That was a remarkably lucid presentation

NOTE Confidence: 0.51398486

00:55:03.727 --> 00:55:05.900 of some very complicated material.

NOTE Confidence: 0.76870465

00:55:09.470 --> 00:55:11.720 Questions. Comments. We have just a

NOTE Confidence: 0.76870465

00:55:11.720 --> 00:55:13.810 couple minutes before official end time.

NOTE Confidence: 0.865789598

00:55:25.040 --> 00:55:27.248 Ellen, I wonder if you could

NOTE Confidence: 0.865789598

00:55:27.248 --> 00:55:28.720 swing back to speculate.

NOTE Confidence: 0.865789598

00:55:28.720 --> 00:55:31.553 Since sort of the motivating you,

NOTE Confidence: 0.865789598

00:55:31.553 --> 00:55:32.764 you've spent a lot of time talking

NOTE Confidence: 0.865789598

00:55:32.764 --> 00:55:34.170 about the framework, the technology,

NOTE Confidence: 0.865789598

00:55:34.170 --> 00:55:36.515 the analytics and the potential and and

NOTE Confidence: 0.865789598

00:55:36.515 --> 00:55:38.925 just a couple slides on the psychedelics.

NOTE Confidence: 0.865789598

00:55:38.930 --> 00:55:40.028 In the middle,

NOTE Confidence: 0.865789598

00:55:40.028 --> 00:55:43.058 which I think is fine because, you know,

NOTE Confidence: 0.865789598

00:55:43.058 --> 00:55:45.956 it's important for us to recognize this.

NOTE Confidence: 0.865789598

00:55:45.960 --> 00:55:47.118 What what what you're working on,

NOTE Confidence: 0.865789598

00:55:47.120 --> 00:55:49.960 but I wonder if you could project OK.

NOTE Confidence: 0.865789598

00:55:49.960 --> 00:55:52.011 This group is motivated primarily by an

NOTE Confidence: 0.865789598

00:55:52.011 --> 00:55:54.279 interest in how do the psychedelics work?

NOTE Confidence: 0.865789598

00:55:54.280 --> 00:55:56.416 Who can they help? You know,

NOTE Confidence: 0.865789598

00:55:56.420 --> 00:55:58.420 how would you imagine over the coming years?

NOTE Confidence: 0.865789598

00:55:58.420 --> 00:55:59.764 And I know you've thought about

NOTE Confidence: 0.865789598

00:55:59.764 --> 00:56:01.155 this a lot because you're doing

NOTE Confidence: 0.865789598

00:56:01.155 --> 00:56:02.560 it and planning on doing it.

NOTE Confidence: 0.865789598

00:56:02.560 --> 00:56:04.966 So how, how would you envision

NOTE Confidence: 0.865789598

00:56:04.966 --> 00:56:07.139 applying this framework to a deep,

NOTE Confidence: 0.865789598

00:56:07.140 --> 00:56:09.304 to developing a deeper

NOTE Confidence: 0.865789598

00:56:09.304 --> 00:56:11.468 understanding of how psychedelics?

NOTE Confidence: 0.865789598

00:56:11.470 --> 00:56:13.042 Affect the brain both in terms

NOTE Confidence: 0.865789598

00:56:13.042 --> 00:56:14.766 of their acute, you know,

NOTE Confidence: 0.865789598

00:56:14.766 --> 00:56:15.702 psychotomimetic, dissociative,

NOTE Confidence: 0.865789598

00:56:15.702 --> 00:56:18.510 whatever effects and in terms of

NOTE Confidence: 0.865789598

00:56:18.574 --> 00:56:21.009 their longer term therapeutic effects.

NOTE Confidence: 0.865789598

00:56:21.010 --> 00:56:24.260 Yeah, so.

NOTE Confidence: 0.865789598

00:56:24.260 --> 00:56:24.770 So there

NOTE Confidence: 0.861475407222222

00:56:24.780 --> 00:56:25.875 there's two pieces of work

NOTE Confidence: 0.861475407222222

00:56:25.875 --> 00:56:27.497 that I didn't have the time to

NOTE Confidence: 0.861475407222222

00:56:27.497 --> 00:56:28.937 highlight and I was wrestling with.

NOTE Confidence: 0.861475407222222

00:56:28.940 --> 00:56:30.452 Do I want to go into them or not?

NOTE Confidence: 0.861475407222222

00:56:30.460 --> 00:56:33.274 And so, so one paper that Katrin

NOTE Confidence: 0.861475407222222

00:56:33.274 --> 00:56:35.000 published is looking at time

NOTE Confidence: 0.861475407222222

00:56:35.000 --> 00:56:36.980 dependent effects on the brain of

NOTE Confidence: 0.861475407222222

00:56:37.048 --> 00:56:39.400 silybin and the same imaging session.

NOTE Confidence: 0.861475407222222

00:56:39.400 --> 00:56:41.792 So one thing that she's done that I

NOTE Confidence: 0.861475407222222

00:56:41.792 --> 00:56:44.175 think is really impressive as shown

NOTE Confidence: 0.861475407222222

00:56:44.175 --> 00:56:46.315 the evolving neural neural effect

NOTE Confidence: 0.861475407222222

00:56:46.315 --> 00:56:48.724 of these compounds in the same

NOTE Confidence: 0.861475407222222

00:56:48.724 --> 00:56:51.175 person and showing how these maps,

NOTE Confidence: 0.861475407222222

00:56:51.175 --> 00:56:53.900 these topographies evolve as we.

NOTE Confidence: 0.861475407222222

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00:56:53.900 --> 00:56:56.235 Selecting data overtime and that

NOTE Confidence: 0.861475407222222

00:56:56.235 --> 00:57:01.020 gives us confidence of the, the, the.

NOTE Confidence: 0.861475407222222

00:57:01.020 --> 00:57:02.256 Basically neural targeting engagement.

NOTE Confidence: 0.861475407222222

00:57:02.256 --> 00:57:04.455 So that's one thing that I think

NOTE Confidence: 0.861475407222222

00:57:04.455 --> 00:57:06.520 we really need more of these neural

NOTE Confidence: 0.861475407222222

00:57:06.520 --> 00:57:08.166 targeting management and so then then

NOTE Confidence: 0.861475407222222

00:57:08.166 --> 00:57:09.678 what Josh has actually done cleverly

NOTE Confidence: 0.861475407222222

00:57:09.680 --> 00:57:12.480 in in a in a sister paper to Lisa's paper,

NOTE Confidence: 0.861475407222222

00:57:12.480 --> 00:57:13.884 which is a whole nother beast

NOTE Confidence: 0.861475407222222

00:57:13.884 --> 00:57:15.459 that I didn't want to get into.

NOTE Confidence: 0.861475407222222

00:57:15.460 --> 00:57:16.900 John senior author on that,

NOTE Confidence: 0.861475407222222

00:57:16.900 --> 00:57:19.168 he's actually taken the the observation

NOTE Confidence: 0.861475407222222

00:57:19.168 --> 00:57:21.177 from Katrina was the observation

NOTE Confidence: 0.861475407222222

00:57:21.177 --> 00:57:24.180 and then fit gene expression to the

NOTE Confidence: 0.861475407222222

00:57:24.180 --> 00:57:26.297 computational models out of John's labs.

NOTE Confidence: 0.861475407222222

00:57:26.300 --> 00:57:26.734 And I,

NOTE Confidence: 0.861475407222222

00:57:26.734 --> 00:57:28.844 I I really didn't want to get into that

NOTE Confidence: 0.861475407222222

00:57:28.844 --> 00:57:31.070 because the the technical detail behind it.

NOTE Confidence: 0.861475407222222

00:57:31.070 --> 00:57:34.206 This is maybe beyond our time scope today,

NOTE Confidence: 0.861475407222222

00:57:34.210 --> 00:57:35.400 but you guys should invite

NOTE Confidence: 0.861475407222222

00:57:35.400 --> 00:57:36.590 him to talk about that.

NOTE Confidence: 0.861475407222222

00:57:36.590 --> 00:57:40.078 And So what he's done is put in

NOTE Confidence: 0.861475407222222

00:57:40.078 --> 00:57:42.254 gradients of 5H2A pharmacology

NOTE Confidence: 0.861475407222222

00:57:42.254 --> 00:57:44.430 into the biophysical models,

NOTE Confidence: 0.861475407222222

00:57:44.430 --> 00:57:44.846 right,

NOTE Confidence: 0.861475407222222

00:57:44.846 --> 00:57:46.926 simulated surrogate models and then

NOTE Confidence: 0.861475407222222

00:57:46.926 --> 00:57:49.407 fit them to individual people given

NOTE Confidence: 0.861475407222222

00:57:49.407 --> 00:57:51.639 LSD and found that actually explains

NOTE Confidence: 0.861475407222222

00:57:51.639 --> 00:57:54.177 the data way better in relation to

NOTE Confidence: 0.861475407222222

00:57:54.177 --> 00:57:56.290 their symptoms that they get acutely.

NOTE Confidence: 0.861475407222222

00:57:56.290 --> 00:57:58.190 So that's that's another paper.

NOTE Confidence: 0.861475407222222

00:57:58.190 --> 00:57:59.870 So these two pieces of work are all

NOTE Confidence: 0.861475407222222

00:57:59.870 --> 00:58:01.130 about neural target engagement.

NOTE Confidence: 0.861475407222222

00:58:01.130 --> 00:58:01.395 Confidence.

NOTE Confidence: 0.861475407222222

00:58:01.395 --> 00:58:02.190 And then Chris,

NOTE Confidence: 0.861475407222222

00:58:02.190 --> 00:58:04.380 your question is how do we apply this?

NOTE Confidence: 0.861475407222222

00:58:04.380 --> 00:58:06.716 What do we do with this in relation

NOTE Confidence: 0.861475407222222

00:58:06.716 --> 00:58:08.870 to helping people who may benefit

NOTE Confidence: 0.861475407222222

00:58:08.870 --> 00:58:10.745 from the the administration of

NOTE Confidence: 0.861475407222222

00:58:10.745 --> 00:58:12.687 these psychedelics and that has

NOTE Confidence: 0.861475407222222

00:58:12.687 --> 00:58:14.937 to do with finding individuals in

NOTE Confidence: 0.861475407222222

00:58:14.940 --> 00:58:17.960 the general population whose?

NOTE Confidence: 0.861475407222222

00:58:17.960 --> 00:58:21.136 Purported or potential neural

NOTE Confidence: 0.861475407222222

00:58:21.136 --> 00:58:23.518 system disturbance alteration,

NOTE Confidence: 0.861475407222222

00:58:23.520 --> 00:58:25.278 whatever term you want to use

NOTE Confidence: 0.861475407222222

00:58:25.278 --> 00:58:27.040 in relation to their behavior.

NOTE Confidence: 0.861475407222222

00:58:27.040 --> 00:58:30.862 In this case mood maps onto that

NOTE Confidence: 0.861475407222222

00:58:30.862 --> 00:58:33.940 neural target engagement profile right.

NOTE Confidence: 0.861475407222222

00:58:33.940 --> 00:58:36.472 And so the question becomes there

NOTE Confidence: 0.861475407222222

00:58:36.472 --> 00:58:39.412 are two questions right that we're

NOTE Confidence: 0.861475407222222

00:58:39.412 --> 00:58:42.224 after is the effect of LSD and or

NOTE Confidence: 0.861475407222222

00:58:42.224 --> 00:58:44.119 silicide been uniform across people.

NOTE Confidence: 0.861475407222222

00:58:44.120 --> 00:58:46.115 In other words if you give it

NOTE Confidence: 0.861475407222222

00:58:46.115 --> 00:58:48.290 to me and you and mark and.

NOTE Confidence: 0.861475407222222

00:58:48.290 --> 00:58:49.412 Anita across.

NOTE Confidence: 0.861475407222222

00:58:49.412 --> 00:58:49.973 Doses.

NOTE Confidence: 0.861475407222222

00:58:49.973 --> 00:58:54.480 Is our brain topography gonna look the same?

NOTE Confidence: 0.861475407222222

00:58:54.480 --> 00:58:55.884 Turns out not,

NOTE Confidence: 0.861475407222222

00:58:55.884 --> 00:58:58.692 that's not true and that matters.

NOTE Confidence: 0.861475407222222

00:58:58.700 --> 00:59:00.548 So for patient precision

NOTE Confidence: 0.861475407222222

00:59:00.548 --> 00:59:02.364 delivery that matters, right,

NOTE Confidence: 0.861475407222222

00:59:02.364 --> 00:59:04.908 because if say you are particularly

NOTE Confidence: 0.861475407222222

00:59:04.908 --> 00:59:07.419 amenable to respond to that compound,

NOTE Confidence: 0.861475407222222

00:59:07.420 --> 00:59:08.248 but I'm not right,

NOTE Confidence: 0.861475407222222

00:59:08.248 --> 00:59:09.670 then you wouldn't give it to me.

NOTE Confidence: 0.861475407222222

00:59:09.670 --> 00:59:12.393 And that has nothing to do with

NOTE Confidence: 0.861475407222222

00:59:12.393 --> 00:59:14.119 my behavioral alteration per se,

NOTE Confidence: 0.861475407222222

00:59:14.120 --> 00:59:16.500 but it may have a lot to do with the

NOTE Confidence: 0.861475407222222

00:59:16.575 --> 00:59:19.559 receptor occupancy and the the nature of the,

NOTE Confidence: 0.861475407222222

00:59:19.560 --> 00:59:20.625 you know, individual.

NOTE Confidence: 0.861475407222222

00:59:20.625 --> 00:59:20.980 Creation.

NOTE Confidence: 0.861475407222222

00:59:20.980 --> 00:59:23.110 Turns out this is unpublished work,

NOTE Confidence: 0.861475407222222

00:59:23.110 --> 00:59:25.406 but ketamine is even more high than.

NOTE Confidence: 0.861475407222222

00:59:25.410 --> 00:59:25.692 Functional,

NOTE Confidence: 0.861475407222222

00:59:25.692 --> 00:59:25.974 right?

NOTE Confidence: 0.861475407222222

00:59:25.974 --> 00:59:28.230 Turns out that there is no one axis

NOTE Confidence: 0.760663160526316

00:59:28.287 --> 00:59:29.423 of the average effect

NOTE Confidence: 0.760663160526316

00:59:29.423 --> 00:59:30.843 Academy on the human brain.

NOTE Confidence: 0.760663160526316

00:59:30.850 --> 00:59:33.202 It's actually highly dimensional,

NOTE Confidence: 0.760663160526316

00:59:33.202 --> 00:59:34.966 which obscures paradoxically

NOTE Confidence: 0.760663160526316

00:59:34.966 --> 00:59:36.963 the average effect, right,

NOTE Confidence: 0.760663160526316

00:59:36.963 --> 00:59:38.128 if you have multiple dimensions.

NOTE Confidence: 0.760663160526316

00:59:38.130 --> 00:59:39.327 And so this is what we're after.

NOTE Confidence: 0.760663160526316

00:59:39.330 --> 00:59:41.540 We're after mapping variation of

NOTE Confidence: 0.760663160526316

00:59:41.540 --> 00:59:42.866 psychopharmacology within and

NOTE Confidence: 0.760663160526316

00:59:42.866 --> 00:59:45.047 across people in order to then

NOTE Confidence: 0.760663160526316

00:59:45.047 --> 00:59:46.587 informed precision of how it

NOTE Confidence: 0.760663160526316

00:59:46.587 --> 00:59:48.298 relates to circuit disturbance.

NOTE Confidence: 0.85620485375

00:59:52.840 --> 00:59:54.412 I don't thank you very much for your call.

NOTE Confidence: 0.85620485375

00:59:54.412 --> 00:59:57.480 I have a question about the study

NOTE Confidence: 0.85620485375

00:59:57.480 --> 01:00:01.026 that you show about the functional

NOTE Confidence: 0.85620485375

01:00:01.026 --> 01:00:05.020 connectivity after LSD and was it in the

NOTE Confidence: 0.85620485375

01:00:05.020 --> 01:00:07.519 acute phase or like post acute or like,

NOTE Confidence: 0.85620485375

111

01:00:07.520 --> 01:00:10.080 I just want to know how long after

NOTE Confidence: 0.85620485375

01:00:10.080 --> 01:00:12.130 those of like any psychedelic,

NOTE Confidence: 0.54301478

01:00:12.200 --> 01:00:15.922 we have a question. And two scans,

NOTE Confidence: 0.54301478

01:00:15.922 --> 01:00:18.400 one at 75 minutes, one at 300 minutes.

NOTE Confidence: 0.54301478

01:00:18.400 --> 01:00:20.826 So you could argue because the ketanserin

NOTE Confidence: 0.54301478

01:00:20.826 --> 01:00:23.689 and the LSD half lives have slightly

NOTE Confidence: 0.54301478

01:00:23.689 --> 01:00:25.619 overlapping and distinct curves.

NOTE Confidence: 0.54301478

01:00:25.620 --> 01:00:27.780 So we wanted one early and one late,

NOTE Confidence: 0.54301478

01:00:27.780 --> 01:00:29.089 and it turns out that that matters.

NOTE Confidence: 0.900398085714286

01:00:30.890 --> 01:00:32.570 So like do you know of any?

NOTE Confidence: 0.900398085714286

01:00:32.570 --> 01:00:35.080 Like is the Hyperconnectivity continues

NOTE Confidence: 0.900398085714286

01:00:35.080 --> 01:00:38.040 after for example after one week?

NOTE Confidence: 0.817742935

01:00:39.430 --> 01:00:40.618 I don't know. We don't know.

NOTE Confidence: 0.817742935

01:00:40.620 --> 01:00:42.077 That's a wide open question, right.

NOTE Confidence: 0.817742935

01:00:42.077 --> 01:00:44.363 So. So I don't know that anybody's

NOTE Confidence: 0.817742935

01:00:44.363 --> 01:00:45.678 looked at these sustained effects.

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01:00:45.680 --> 01:00:47.857 What we have some stuff from Arena

01:00:47.860 --> 01:00:49.212 Australia's data set, right.

01:00:49.212 --> 01:00:51.560 Which again I it's it's really her

01:00:51.560 --> 01:00:53.366 story to report but but it turns

01:00:53.366 --> 01:00:54.993 out also when we give ketamine

01:00:54.993 --> 01:00:56.937 and look at people a day later,

01:00:56.937 --> 01:00:59.079 right, with F MRI and behavior,

01:00:59.080 --> 01:01:00.720 there's this and you guys know this, right.

01:01:00.720 --> 01:01:02.940 There's this crazy inverted V relationship.

01:01:02.940 --> 01:01:05.691 Some people have a sustained effect of

01:01:05.691 --> 01:01:07.513 the antidepressant phenomenon and other

01:01:07.513 --> 01:01:09.825 people go right back to where they were.

01:01:09.830 --> 01:01:11.545 And we don't know why this is.

01:01:11.550 --> 01:01:14.160 This is unexplored neurobehavioral effects.

01:01:14.160 --> 01:01:15.330 We don't know,

01:01:15.330 --> 01:01:17.280 but we know that everybody

NOTE Confidence: 0.817742935

01:01:17.280 --> 01:01:19.058 acutely shows some kind of.

NOTE Confidence: 0.817742935

01:01:19.060 --> 01:01:19.722 Clinical efficacy,

NOTE Confidence: 0.817742935

01:01:19.722 --> 01:01:22.742 but then a day later you have this rebound

NOTE Confidence: 0.817742935

01:01:22.742 --> 01:01:25.496 and who is rebounding and who is not why?

NOTE Confidence: 0.817742935

01:01:25.500 --> 01:01:27.762 You know there's ideas about synaptic

NOTE Confidence: 0.817742935

01:01:27.762 --> 01:01:29.700 plasticity and LTP like phenomena

NOTE Confidence: 0.817742935

01:01:29.700 --> 01:01:32.255 and and you know which people have

NOTE Confidence: 0.817742935

01:01:32.255 --> 01:01:33.801 that dendritic proliferation would

NOTE Confidence: 0.817742935

01:01:33.801 --> 01:01:36.063 then stabilizes and who is most

NOTE Confidence: 0.817742935

01:01:36.063 --> 01:01:38.692 likely to benefit from that kind

NOTE Confidence: 0.817742935

01:01:38.692 --> 01:01:40.440 of and you know psychedelics and

NOTE Confidence: 0.817742935

01:01:40.440 --> 01:01:41.720 ketamine very different from ecology,

NOTE Confidence: 0.817742935

01:01:41.720 --> 01:01:42.049 very,

NOTE Confidence: 0.817742935

01:01:42.049 --> 01:01:44.023 very different but maybe converging on

NOTE Confidence: 0.817742935

01:01:44.023 --> 01:01:46.054 some endpoint of exciting and driving

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NOTE Confidence: 0.817742935

01:01:46.054 --> 01:01:48.357 the circuits into an LTP like phenomena,

NOTE Confidence: 0.817742935

01:01:48.360 --> 01:01:49.491 we don't know.

NOTE Confidence: 0.817742935

01:01:49.491 --> 01:01:49.868 And

NOTE Confidence: 0.873927528888889

01:01:49.880 --> 01:01:51.576 is there any relationship,

NOTE Confidence: 0.873927528888889

01:01:51.576 --> 01:01:53.272 any association between the

NOTE Confidence: 0.873927528888889

01:01:53.272 --> 01:01:55.560 degree of this hyperconnectivity

NOTE Confidence: 0.873927528888889

01:01:55.560 --> 01:01:57.008 and response to treatment?

NOTE Confidence: 0.744778377058824

01:01:57.880 --> 01:02:00.466 We don't know that's nobody has

NOTE Confidence: 0.744778377058824

01:02:00.466 --> 01:02:02.751 that data set again nobody's

NOTE Confidence: 0.744778377058824

01:02:02.751 --> 01:02:05.577 done MD either you know major,

NOTE Confidence: 0.744778377058824

01:02:05.580 --> 01:02:08.044 major depression or you know severe mood

NOTE Confidence: 0.744778377058824

01:02:08.044 --> 01:02:10.156 disturbance data set or experiment in

NOTE Confidence: 0.744778377058824

01:02:10.156 --> 01:02:12.498 which people were given either ketamine,

NOTE Confidence: 0.744778377058824

01:02:12.498 --> 01:02:16.061 indoor silybin or randomized to one of

NOTE Confidence: 0.744778377058824

01:02:16.061 --> 01:02:19.238 these arms scanned prior at baseline.

NOTE Confidence: 0.744778377058824

01:02:19.240 --> 01:02:20.580 Scanned acutely scanned post

NOTE Confidence: 0.744778377058824

01:02:20.580 --> 01:02:22.590 and then scanned later when they

NOTE Confidence: 0.744778377058824

01:02:22.648 --> 01:02:24.543 either sustain their recovered and

NOTE Confidence: 0.744778377058824

01:02:24.543 --> 01:02:26.438 understood what predicts it right.

NOTE Confidence: 0.744778377058824

01:02:26.440 --> 01:02:27.488 Like wide open question.

NOTE Confidence: 0.744778377058824

01:02:27.488 --> 01:02:29.384 And I think our department is unique

NOTE Confidence: 0.744778377058824

01:02:29.384 --> 01:02:31.004 position to go after this right.

NOTE Confidence: 0.744778377058824

01:02:31.010 --> 01:02:32.620 I think there's plenty of

NOTE Confidence: 0.744778377058824

01:02:32.620 --> 01:02:34.700 people who have the the means,

NOTE Confidence: 0.744778377058824

01:02:34.700 --> 01:02:36.368 expertise and talent to go after

NOTE Confidence: 0.744778377058824

01:02:36.368 --> 01:02:38.177 this and it's a fascinating question

NOTE Confidence: 0.744778377058824

01:02:38.177 --> 01:02:40.721 like this is what we need to know.

NOTE Confidence: 0.744778377058824

01:02:40.730 --> 01:02:42.649 Thank you. No, my pleasure.

NOTE Confidence: 0.69949868

01:02:44.520 --> 01:02:46.220 Anahita stole my question.

NOTE Confidence: 0.69949868

01:02:46.220 --> 01:02:48.459 I I also had the question about can

NOTE Confidence: 0.69949868

01:02:48.460 --> 01:02:50.259 we predict who was going to respond

NOTE Confidence: 0.69949868

01:02:50.260 --> 01:02:52.120 if they have a certain a certain

NOTE Confidence: 0.69949868

01:02:52.120 --> 01:02:55.298 pattern that that that that shows up.

NOTE Confidence: 0.69949868

01:02:55.300 --> 01:02:57.332 But I also wonder whether there have

NOTE Confidence: 0.69949868

01:02:57.332 --> 01:02:58.486 been other neuroimaging studies,

NOTE Confidence: 0.69949868

01:02:58.486 --> 01:03:00.199 not with psychedelics but with

NOTE Confidence: 0.69949868

01:03:00.200 --> 01:03:02.384 other treatments that showed

NOTE Confidence: 0.69949868

01:03:02.384 --> 01:03:04.644 changes in the connectivity such

NOTE Confidence: 0.52348149

01:03:04.660 --> 01:03:08.544 as T or presence. Totally, totally.

NOTE Confidence: 0.52348149

01:03:08.544 --> 01:03:09.760 So actually I forgot.

NOTE Confidence: 0.52348149

01:03:09.760 --> 01:03:12.160 So charity of Donna did a nice study

NOTE Confidence: 0.52348149

01:03:12.160 --> 01:03:14.827 where he looked at meta analysis of of.

NOTE Confidence: 0.52348149

01:03:14.830 --> 01:03:16.944 Uh, effects of ketamine. I don't wanna,

NOTE Confidence: 0.52348149

01:03:16.950 --> 01:03:18.924 I actually don't wanna forget that I

NOTE Confidence: 0.52348149

01:03:18.924 --> 01:03:20.836 think John's on the paper, John Christow.

NOTE Confidence: 0.52348149

01:03:20.836 --> 01:03:22.700 So there is some evidence of this in

NOTE Confidence: 0.52348149

01:03:22.754 --> 01:03:24.446 the literature that people have done,

NOTE Confidence: 0.52348149

01:03:24.450 --> 01:03:26.124 but just not the experiments that

NOTE Confidence: 0.52348149

01:03:26.124 --> 01:03:27.870 you guys were asking about that.

NOTE Confidence: 0.52348149

01:03:27.870 --> 01:03:29.290 But to your point, yes.

NOTE Confidence: 0.52348149

01:03:29.290 --> 01:03:31.834 In fact, we worked with Anil Malhotra and

NOTE Confidence: 0.52348149

01:03:31.834 --> 01:03:34.529 to look at the effect of clozapine, right.

NOTE Confidence: 0.52348149

01:03:34.529 --> 01:03:35.724 We're actually writing this up

NOTE Confidence: 0.52348149

01:03:35.724 --> 01:03:36.970 for publication as we speak.

NOTE Confidence: 0.52348149

01:03:36.970 --> 01:03:37.672 And so, yes,

NOTE Confidence: 0.52348149

01:03:37.672 --> 01:03:39.310 in fact you can predict and and

NOTE Confidence: 0.52348149

01:03:39.363 --> 01:03:41.519 turns out that these are very strong

NOTE Confidence: 0.52348149

01:03:41.519 --> 01:03:43.104 effects actually when you get

NOTE Confidence: 0.52348149

01:03:43.104 --> 01:03:44.872 people who are responding, right.

NOTE Confidence: 0.52348149

01:03:44.872 --> 01:03:48.158 The neural maps of predicting who responds

NOTE Confidence: 0.52348149

01:03:48.158 --> 01:03:50.234 are actually quite nice and clean.

NOTE Confidence: 0.52348149

01:03:50.240 --> 01:03:52.718 It's just that these are small samples

NOTE Confidence: 0.52348149

01:03:52.718 --> 01:03:54.497 like we're talking 141520 people, right.

NOTE Confidence: 0.52348149

01:03:54.497 --> 01:03:56.170 So it's just the first wave of

NOTE Confidence: 0.52348149

01:03:56.221 --> 01:03:57.574 work that's coming out, right?

NOTE Confidence: 0.52348149

01:03:57.574 --> 01:03:59.338 Like this is the next generation,

NOTE Confidence: 0.52348149

01:03:59.340 --> 01:03:59.763 right.

NOTE Confidence: 0.52348149

01:03:59.763 --> 01:04:01.878 They don't like precision pharmacology

NOTE Confidence: 0.52348149

01:04:01.878 --> 01:04:04.062 to dissect individual variation in

NOTE Confidence: 0.52348149

01:04:04.062 --> 01:04:05.778 relation to neurobehavioral effects.

NOTE Confidence: 0.52348149

01:04:05.780 --> 01:04:07.790 Like, I I'm just super excited,

NOTE Confidence: 0.52348149

01:04:07.790 --> 01:04:08.051 right,

NOTE Confidence: 0.52348149

01:04:08.051 --> 01:04:09.878 because I think this is actually happening.

NOTE Confidence: 0.52348149

01:04:09.880 --> 01:04:11.364 Like we actually see this now like

NOTE Confidence: 0.52348149

01:04:11.364 --> 01:04:13.179 the next 5 to 10 years as possible.

NOTE Confidence: 0.8752906

01:04:16.220 --> 01:04:16.890 Great. Thanks.

NOTE Confidence: 0.781236963333333

01:04:20.000 --> 01:04:23.618 Very excited. I'm sorry, go ahead.

NOTE Confidence: 0.781236963333333

01:04:23.620 --> 01:04:25.321 I was just going to say we're

NOTE Confidence: 0.781236963333333

01:04:25.321 --> 01:04:26.612 overtime and I wonder if

NOTE Confidence: 0.781236963333333

01:04:26.612 --> 01:04:28.106 we should wrap up that if.

NOTE Confidence: 0.781236963333333

01:04:28.110 --> 01:04:29.846 Well, I was just going to say,

NOTE Confidence: 0.781236963333333

01:04:29.850 --> 01:04:31.190 I'll make it quick then.

NOTE Confidence: 0.781236963333333

01:04:31.190 --> 01:04:32.219 So very exciting

NOTE Confidence: 0.789216434

01:04:32.230 --> 01:04:37.230 work, great presentation and the

NOTE Confidence: 0.789216434

01:04:37.230 --> 01:04:39.960 several questions that were just

NOTE Confidence: 0.789216434

01:04:39.960 --> 01:04:42.921 asked made me think about some of our

NOTE Confidence: 0.789216434

01:04:42.921 --> 01:04:44.612 work in the psychotherapy Development

NOTE Confidence: 0.789216434

01:04:44.612 --> 01:04:47.489 Center and the data that we've been

NOTE Confidence: 0.789216434

01:04:47.489 --> 01:04:49.450 collecting over the past 15 years

NOTE Confidence: 0.789216434

01:04:49.450 --> 01:04:51.440 by integrating F MRI measures into

NOTE Confidence: 0.789216434

01:04:51.440 --> 01:04:53.462 randomized clinical trials and the

NOTE Confidence: 0.789216434

01:04:53.462 --> 01:04:55.326 potential for these approaches we've

NOTE Confidence: 0.789216434

01:04:55.326 --> 01:04:57.600 been using things like connectome based.

NOTE Confidence: 0.789216434

01:04:57.600 --> 01:04:59.000 Predictive modeling, but there

NOTE Confidence: 0.8450367575

01:04:59.010 --> 01:05:02.800 are many different approaches to understand

NOTE Confidence: 0.950403578571429

01:05:03.270 --> 01:05:07.988 better how people may respond to treatment.

NOTE Confidence: 0.950403578571429

01:05:07.990 --> 01:05:11.665 So I think again very exciting work

NOTE Confidence: 0.950403578571429

01:05:11.670 --> 01:05:15.478 would be great to to speak further.

NOTE Confidence: 0.950403578571429

01:05:15.480 --> 01:05:17.470 Because I think that we are at a

NOTE Confidence: 0.950403578571429

01:05:17.470 --> 01:05:19.635 stage and as you mentioned uniquely

NOTE Confidence: 0.950403578571429

01:05:19.635 --> 01:05:22.365 positioned within our department to

NOTE Confidence: 0.950403578571429

01:05:22.365 --> 01:05:24.860 make significant contributions to the

NOTE Confidence: 0.950403578571429

01:05:24.860 --> 01:05:27.212 understanding of how we might best

NOTE Confidence: 0.950403578571429

01:05:27.212 --> 01:05:29.056 advance psychiatric care for people.

NOTE Confidence: 0.950403578571429

01:05:29.056 --> 01:05:30.816 I couldn't agree more mark.

NOTE Confidence: 0.950403578571429

01:05:30.820 --> 01:05:33.948 And I think that your point there's many

NOTE Confidence: 0.950403578571429

01:05:33.948 --> 01:05:36.419 different ways that we'll all be in some

NOTE Confidence: 0.950403578571429

01:05:36.419 --> 01:05:38.557 family of general linear models, right.

NOTE Confidence: 0.950403578571429

01:05:38.557 --> 01:05:40.459 So and and people can approach

NOTE Confidence: 0.950403578571429

01:05:40.459 --> 01:05:41.880 this from various angles.

NOTE Confidence: 0.950403578571429

01:05:41.880 --> 01:05:43.714 I think that you know to your

NOTE Confidence: 0.950403578571429

01:05:43.714 --> 01:05:45.420 point it's going to be the data.

NOTE Confidence: 0.950403578571429

01:05:45.420 --> 01:05:47.380 That you guys have and we're going to

NOTE Confidence: 0.950403578571429

01:05:47.380 --> 01:05:49.298 continue to collect and it's going to

NOTE Confidence: 0.950403578571429

01:05:49.298 --> 01:05:51.005 be about the right behavioral response

NOTE Confidence: 0.950403578571429

01:05:51.005 --> 01:05:53.229 mapping which all of you are alluding to.

NOTE Confidence: 0.950403578571429

01:05:53.230 --> 01:05:56.119 So I I couldn't agree more and I think

NOTE Confidence: 0.950403578571429

01:05:56.119 --> 01:05:59.290 it's just it's it's just kind of you know.

NOTE Confidence: 0.950403578571429

01:05:59.290 --> 01:06:00.420 Maybe it's the sunny day,

NOTE Confidence: 0.950403578571429

01:06:00.420 --> 01:06:01.948 so I feel optimistic,

NOTE Confidence: 0.950403578571429

01:06:01.948 --> 01:06:05.632 but but I I I genuinely think that this

NOTE Confidence: 0.950403578571429

01:06:05.632 --> 01:06:08.466 was not possible 15 years ago, right?

NOTE Confidence: 0.950403578571429

01:06:08.466 --> 01:06:10.500 Like we didn't have the tech to do this

NOTE Confidence: 0.950403578571429

01:06:10.559 --> 01:06:12.674 and we actually now not only have the tech,

122

NOTE Confidence: 0.950403578571429

01:06:12.680 --> 01:06:14.420 but the information to do it.

NOTE Confidence: 0.950403578571429

01:06:14.420 --> 01:06:15.848 And so I want to just leave

NOTE Confidence: 0.950403578571429

01:06:15.848 --> 01:06:16.740 people with that idea,

NOTE Confidence: 0.950403578571429

01:06:16.740 --> 01:06:20.730 right, that that you know.

NOTE Confidence: 0.950403578571429

01:06:20.730 --> 01:06:22.613 And the fact that Yale is really

NOTE Confidence: 0.950403578571429

01:06:22.613 --> 01:06:23.793 stepping up into psychedelic

NOTE Confidence: 0.950403578571429

01:06:23.793 --> 01:06:25.984 medicine and and that you guys are

NOTE Confidence: 0.950403578571429

01:06:25.984 --> 01:06:27.938 doing this work and I couldn't

NOTE Confidence: 0.950403578571429

01:06:27.938 --> 01:06:29.523 be more supportive and whatever,

NOTE Confidence: 0.950403578571429

01:06:29.530 --> 01:06:31.350 whatever you need on on,

NOTE Confidence: 0.950403578571429

01:06:31.350 --> 01:06:32.040 happy to help.

NOTE Confidence: 0.891830826

01:06:36.300 --> 01:06:37.692 So with that, I think we

NOTE Confidence: 0.891830826

01:06:37.692 --> 01:06:39.190 should close for today. Alan.

NOTE Confidence: 0.891830826

01:06:39.190 --> 01:06:42.830 Thank you again for being here with us

NOTE Confidence: 0.891830826

01:06:42.830 --> 01:06:45.540 today and for covering this material.

NOTE Confidence: 0.891830826

01:06:45.540 --> 01:06:48.120 I believe next month, tentatively,

NOTE Confidence: 0.891830826

01:06:48.120 --> 01:06:50.164 Cyril has agreed to present either he

NOTE Confidence: 0.891830826

01:06:50.164 --> 01:06:52.429 or someone from his group or about some

NOTE Confidence: 0.891830826

01:06:52.429 --> 01:06:54.420 of the work that they've been doing,

NOTE Confidence: 0.891830826

01:06:54.420 --> 01:06:55.398 perhaps about DMT,

NOTE Confidence: 0.891830826

01:06:55.398 --> 01:06:58.040 where they've done some of the first work,

NOTE Confidence: 0.891830826

01:06:58.040 --> 01:06:59.846 both in health and in individuals

NOTE Confidence: 0.891830826

01:06:59.846 --> 01:07:01.293 with depressions. That'd be exciting.

NOTE Confidence: 0.891830826

01:07:01.293 --> 01:07:02.417 That's not confirmed yet,

NOTE Confidence: 0.891830826

01:07:02.420 --> 01:07:05.521 but we'll send out emails once we

NOTE Confidence: 0.891830826

01:07:05.521 --> 01:07:07.968 have a confirmation and a title

NOTE Confidence: 0.891830826

01:07:07.968 --> 01:07:10.369 and hope to see you all then.

NOTE Confidence: 0.891830826

01:07:10.370 --> 01:07:11.699 Take care, everybody.