Episode Book

EPISODE #6649

Brain implants for depression and the two-millimetre gap

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SYNOPSIS

Deep brain stimulation is approved for Parkinson's, tremor, and OCD, yet it remains unapproved for treatment-resistant depression. This look at the science traces Helen Mayberg's work on Area 25, the surprising failures of St. Jude Medical's BROADEN and Medtronic's RECLAIM trials, and a new Canadian sham-controlled study where unstimulated patients initially outperformed active ones. It explores how tractography imaging revealed that shifting an electrode by just two millimetres changes which white-matter tracts are engaged, turning the same surgery into two different treatments.

TRANSCRIPT



Corn

A surgeon drills two small holes in your skull, threads electrodes down into the brain, and wires them to a battery in your chest. The goal: to lift a depression that twenty years of medication never touched. It sounds like either the future of psychiatry or its cautionary tale, and here's the thing — it's been both, twice.



Corn

That's roughly where Daniel's prompt begins. He wants the whole arc of deep brain stimulation for treatment-resistant depression — why anyone thought it would work, what happened in the big sham-controlled trials, the ones that failed and the later results that revived the field, and where things stand now with personalised and closed-loop devices.



Corn

One footnote before we start. Daniel usually picks the topics himself, but this one came out of a rare reverse — he asked the friendly AI down the road what the show might be missing, the corners of mental health nobody talks about, and this is what came back. So if you've been waiting for us to go here, you have company.



Herman

And it's a good time to go here, because the field is in motion. We've got a new sham-controlled trial this year, we've got ultrasound knocking on the door from the outside. But let's set the stage, because DBS itself is not experimental — it's boring, in the best sense.



Herman

The hardware is a pulse generator implanted under the skin of the chest, leads running up to electrodes sitting in specific spots in the brain, delivering controlled electrical impulses. Over two hundred and forty-four thousand people have been implanted worldwide in three decades, mostly for Parkinson's, essential tremor, dystonia. The FDA has approved it for tremor since ninety-seven, Parkinson's since two thousand two, dystonia, OCD, epilepsy.



Corn

Everything except the one we're talking about.



Herman

Right. Depression is the studied-but-never-approved indication, and that gap is the whole story. Now, treatment-resistant depression itself — the standard definition is major depression that hasn't responded adequately to at least two different antidepressants, at a decent dose, for a decent duration. Inadequate response usually means less than a twenty-five percent reduction in symptoms.



Corn

A quarter. Two full drug trials and you're a quarter better.



Herman

At best, yes. And nearly thirty percent of people with major depression fall into that bucket. We're not talking about a rare fringe — this is a huge population, and by some estimates around a hundred million people worldwide.



Corn

So the stakes are enormous, the patient pool is enormous, and the surgery is approved for five other things. Why isn't this settled?



Herman

Because the brain doesn't care how the petition is worded. The story starts with a neuroscientist named Helen Mayberg and a piece of tissue called Area 25.



Herman

The subgenual cingulate — Area 25 — is a pair of pale-pink curves sitting underneath the corpus callosum, each about the size and shape of a newborn's crooked finger. Mayberg's work going back to her imaging studies suggested that in depressed people this region is hyperactive — a junction box stuck broadcasting despair. And her model wasn't the old



Herman (continued)

chemical-imbalance story. It was a circuit story: depression as specific networks locked in a pathological pattern, not a global shortage of serotonin.



Corn

Which reframes what you're trying to do. You're not topping up a tank.



Herman

No. You're interrupting a signal. And here's what I find elegant — and I want to be careful with that word, because elegant mechanisms have burned this field before —



Corn

Noted for the record.



Herman

The mechanism is thought to be disruption. You're not stimulating an underactive area back to life, the pacemaker metaphor everyone reaches for. You're mimicking what a lesion would do — disrupting pathologically elevated, oversynchronised traffic in a misfiring network — but reversibly. Turn it off, the effect goes away. Unlike ablation, nobody's burning a bridge.



Corn

That reversibility is what makes it science, isn't it. You can run a blinded trial because you can switch the thing off without the patient knowing.



Herman

And that's rare in surgery! It's one of the few neurosurgical procedures that even permits a proper double-blind design. Keep that in the back of your mind, because it becomes the instrument of the field's humiliation.



Herman

So, two thousand three to two thousand six. Mayberg tries the surgery on twenty people who had been torturously depressed for years despite every treatment that exists. In two thousand five she publishes the first six — who did amazingly well. The other fourteen later showed similar progress. Most cut their depression scores by around half. Over a third left depression behind entirely.



Corn

For people who'd tried everything, a third in remission is... that's not a marginal result.



Herman

It was seismic. Tom Insel, then director of the National Institute of Mental Health, called it a new way of understanding depression. And the momentum was real — St. Jude Medical designed a trial called BROADEN, which stood for Brodmann Area twenty-five deep brain neuromodulation, very proud of that. The plan was two hundred patients across twenty neurosurgery centres, devices in everyone, turned on in two-thirds, off in one-third, and nobody with patient contact would know which was which.



Corn

Textbook.



Herman

Textbook. What they got was ninety patients, and the trial published in Lancet Psychiatry in twenty seventeen. Sixty active, thirty sham, six months. The response rate, averaged over months four through six — twenty percent active, seventeen percent sham. Not statistically significant. Three points.



Corn

Three points is a rounding error wearing a lab coat.



Herman

The futility analysis is where it gets painful. The statisticians had predicted a forty percent response in the stimulation group against eighteen and a half in controls. Actual: twenty against seventeen. The model concluded the trial had a seventeen percent chance of success if it continued. That didn't technically meet the pre-set futility threshold — but the sponsor ended enrolment anyway.



Corn

Ninety patients instead of two hundred. If they'd needed those numbers, "seventeen percent chance of success" is a kind sentence.



Herman

It is. And RECLAIM, the Medtronic-sponsored trial, went the same way, maybe worse. That one targeted the ventral capsule and ventral striatum — the internal capsule, the reward circuitry region. All thirty patients got implants; everyone went through an optimisation phase first, hunting for stimulation settings that produced acute mood effects. Then half had their devices switched off for four months. The blind was verified — it held. And the review board stopped the trial because the data showed no sign the stimulation was helping.



Corn

Define "no sign."



Herman

The patients who weren't being stimulated improved more than the patients who were.



Corn

The machine made it worse.



Herman

Numerically, in that window, yes. That's the sentence that should keep anyone in this field awake.



Corn

And now, a brief call from Corn's mother. Dorothy, are you there?

D

Dorothy

Hello dear, it's your mother, with Dorothy's History of Toast.

D

Dorothy

The pop-up toaster was invented by Charles Strite, a mechanic in Minnesota, who was fed up with the burnt toast in his factory canteen. He filed the patent in nineteen nineteen.

D

Dorothy

And I suppose that's the way of it, dear, a man fixes one thing and the rest of the world carries on burning its breakfast.

D

Dorothy

Anyway, I've got a load of washing on and I should see to it. Give my love to Herman. Bye bye now.



Herman

Give her my love back, Corn.



Corn

She's got a load of washing on, Herman, she's busy.



Herman

Fair enough. Where were we — sham beating active. So here's the temptation, and I want to name it because a lot of coverage falls into it: the temptation is to say the trials were rigged, or that the blind leaked, and therefore the open-label results were right all along. But the sham problem cuts both ways, and it got stranger this year.



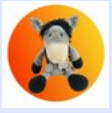
Herman

The Canadian trial, published this year, thirty-five patients, single centre — the largest single-centre sham-controlled study in the literature. Crossover design: two three-month phases, everyone eventually gets stimulation, randomised order. No significant difference between groups at three months or six months. All groups improved. And at the end of the blinded phase, the group that had been off the whole time — the OFF-OFF group — had numerically lower depression scores than the group that had been on the whole time.



Corn

The group that got the least treatment did the best. Again.



Herman

Within the blinded window. Then you flip to the open-label follow-up, everyone's device on, and the response rates are sixty-five point seven percent at twelve months, sixty-nine at eighteen, seventy-three at twenty-four. Cognitive testing showed no deterioration — one measure, category fluency, actually improved after three months of active stimulation, though that didn't survive multiple-comparison correction, so I'd file it under interesting, not established.



Corn

Herman, sit with that pair of numbers for a second. Blinded: nothing. Open-label: three-quarters responding at two years. What do you actually do with that as a clinician? You spent decades in medicine — how do you hold both?



Herman

Honestly? Uncomfortably. There are three live explanations and none of them is comfortable. One: the blind is doing something strange — there may be perceptible effects of stimulation that let patients figure out their assignment, and once someone believes they're in the active arm, expectation does the rest. Two: regression to the mean and natural course are enormous in a population this severe, people enrol at their worst. Three: the active stimulation in those trials wasn't hitting the right circuits for those particular brains, and the benefits only emerge after months of individualised tuning — tuning that happened during the open-label phase, after the blinded window had closed.



Corn

And that third one is the explanation the field itself chose to run with.



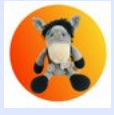
Herman

Because there's evidence for it. And this is where the revival begins. Between 2008 and 2012 — the BROADEN era — targeting meant fixed anatomical coordinates. Same spot, every brain, on the theory that Area 25 is Area 25. What tractography imaging has since shown is that what predicts benefit isn't the grey matter point — it's which white-matter tracts your electrodes happen to sit near and engage. The bundles of cables, not the junction box. Two patients can have electrodes a couple of millimetres apart, in the same named region, and be getting entirely different treatments.



Corn

So the same surgery, two millimetres apart, is two different drugs.



Herman

That's the cleanest way to put it I know. And it explains the trial failures without declaring the mechanism dead: a fixed coordinate in a heterogeneous population means some fraction of implanted patients got a well-placed intervention and a larger fraction got, effectively, a near miss. Averaged together, that washes out against sham.



Corn

I'd like to push on something, though. The wash-out explanation assumes the near-miss is neutral. But in RECLAIM the unstimulated patients did better than the stimulated ones. A near miss isn't zero — it's slightly negative.



Herman

That's a fair hit, and I don't have a clean answer. Stimulation at an unhelpful site isn't necessarily harmless — there can be mood effects, anxiety, agitation when you're in the wrong tract. My guess is it's a mix of small negative effects in some, nothing in most, and the whole thing swamped by regression to the mean in a group of thirty. But you're right that "the targeting was just off" shouldn't be waved around as if it explains everything cleanly.



Corn

So the trials failed. But the field didn't abandon the idea — it went back to the drawing board on targeting, and that's where the revival comes from.



Herman

And the revival has two prongs. The first is connectomic targeting with recording devices, and the landmark is the twenty twenty-three Nature paper from Alagapan and colleagues. Ten patients, subgenual cingulate DBS, but with a new generation of device that can record the local electrical activity — the local field potential — while stimulating. At twenty-four weeks, ninety percent showed a robust clinical response. Seventy percent were in remission.



Corn

Ninety and seventy. In the same disease where the big trials couldn't beat sham by three points.



Herman

And open-label, yes — hold that caveat, it's load-bearing. But the recording is the real news. Using signals from six of the participants, they ran an explainable AI approach to find changes in the local field potential that tracked the patient's actual clinical state — a biomarker. Distinct from the transient artefact of stimulation itself, sensitive when the clinicians adjusted the therapy, accurate at capturing each person's recovery. For the first time, the device isn't just delivering current and hoping — it's reading the circuit back.



Corn

Which answers the other problem Daniel's prompt gestures at — how do you measure depression objectively? The clinic's instrument is a questionnaire and a sad conversation.



Herman

And subjective symptom reporting is exactly what the review literature flags as a bottleneck — the twenty twenty-four Molecular Psychiatry review by Johnson, Okun, Scangos and colleagues says the effectiveness has been demonstrated in meta-analyses and open-label work but the randomised trials are mixed, and one of the key challenges is tracking symptoms objectively to evaluate the therapy. If the biomarker work holds up, you can dose against a signal instead of against a mood scale.



Corn

There was a lovely detail in that study too — recovery predicted before anyone switched anything on.



Herman

Yes — the variable recovery trajectories were predicted by the degree of preoperative damage to the structural integrity and connectivity of the targeted white-matter network. Read that again: how well you do was partly visible in the wiring before the surgery. Which immediately raises the obvious clinical question — should you implant at all in the patients whose networks look badly damaged? That's a selection question, and the field is starting to answer it. A twenty twenty-four study of nineteen patients found that regional brain glucose metabolism predicted response with eighty-four percent accuracy — better than blood flow or grey-matter volume, both around seventy-four. And a -analysis of machine-learning models in this space pooled sensitivity of about zero point seven four. Not good enough to deny someone surgery, but good enough to start a conversation about who's a good candidate.



Corn

And that matters because this is not a risk-free intervention. You're drilling a skull.



Herman

The second prong is the closed-loop approach, and I want to be very precise about its status, because it's the part that gets over-sold. There is exactly one published individual. Nature Medicine, twenty twenty-one. A woman with treatment-resistant depression, and the workup was extraordinary — days of intracranial recording and focal stimulation across multiple sites, mapping which contacts produced which emotional responses, to find a personalised biomarker and a personalised treatment location.



Corn

What was her biomarker?



Herman

Gamma activity — fast oscillations — in the amygdala, appearing when her depressive symptoms came on. The treatment site was the ventral capsule and ventral striatum, the reward-circuitry region that RECLAIM had targeted with such disappointment. They implanted a chronic sensing-and-stimulating device, and when the amygdala signature appeared, it delivered about one milliamp at that site. On demand, only when needed.



Corn

A demand pacemaker for mood.



Herman

And she had rapid and sustained improvement. But the authors themselves are explicit that generalisation requires further work. One person. One biomarker, one site, one wiring diagram that is hers. The follow-up protocol now being used — the staged workup — involves implanting ten recording electrodes across five brain regions bilaterally and monitoring for days before you even choose the permanent target. This is bespoke medicine in the most literal sense: the intervention is designed after the implant, not before.



Corn

Which is a strange sentence. Usually you design the treatment and then give it to the patient.



Herman

It's the inversion. And that inversion is expensive, it's slow, it's a hospitalisation — and it might be the only honest way to do it, if the disease really is heterogeneous. That's the definition problem sitting underneath everything. Treatment-resistant depression is defined by failing two antidepressants. Not by any biology — by a treatment history. It's entirely possible that the label covers several different circuit disorders that all present as depression, in which case a fixed target was never going to work for everyone, and the connectomic, closed-loop approaches aren't a refinement — they're the acknowledgement that the category itself was too coarse.



Corn

We touched this exact nerve in the episode about whether therapy and pills produce brain changes that last — the question there was whether the intervention rewrites the circuit or rides on it. Here it's the same question with the skull open. Corn... sorry, Herman, that's yours.



Herman

It is, and the honest version is nobody knows yet whether DBS for depression rewires anything permanently or whether it's a very expensive ongoingsubscription. The two-year open-label data says the benefit persists while the device works — that's what we can say.



Corn

Now the part I've been waiting for. The outsiders.



Herman

The ultrasound work! Yes. Two strands, and both matter. The first, published last year in Biological Psychiatry: twenty-two people with treatment-resistant depression, randomised, double-blind, sham-controlled — low-intensity focused ultrasound aimed at the subgenual cingulate from outside the head. Functional MRI during stimulation showed a target-specific decrease in SCC activity — that's real engagement of the same region all the electrodes are aimed at — and in the per-protocol sample, real stimulation beat sham on depression scores at twenty-four hours.



Corn

Sham-controlled. Positive. Those four words haven't appeared together in this episode yet.



Herman

In the non-invasive arm, they have. And the second strand is wilder — the first human use of metalens-based transcranial ultrasound. The problem with getting ultrasound through a skull is that bone distorts the beam, so this group used patient-specific metamaterials — a lens 3D-printed to correct for each person's skull aberrations — targeting the individual's white-matter tracts of the subgenual cingulate. Note that: tract-based targeting, the same lesson the electrode people learned, applied from outside the head.



Corn

How many people?



Herman

Five. Open-label. Five days, twenty-five sessions of five minutes each. By day five, depression severity down an average of sixty-one percent, range thirty to eighty-four. No serious adverse events.



Corn

Five days. The electrode people need two years of tuning.



Herman

I would put a hand on that enthusiasm — five people, open-label, and we've spent this whole episode learning exactly what five people and an open-label design can do to your judgement. Mayberg's first six patients also did amazingly well. But the direction of travel is what matters: if you can reach the deep circuits without drilling, the entire risk-benefit calculation changes. No haemorrhage risk, no battery replacements, no lead revisions — and a hundred million people worldwide with this condition. The authors make exactly that point: implantation poses significant risks and limits widespread use. You cannot scale brain surgery to a hundred million people. You can scale a clinic with an ultrasound wand and a printed lens.



Corn

And if the dose is five days rather than two years of programming, you can run the trials faster and cheaper too.



Herman

The trials are the choke point for everything. Where does the science actually stand, November twenty twenty-six? No published, adequately powered, positive randomised sham-controlled trial of subgenual cingulate DBS for treatment-resistant depression. None. No regulatory approval anywhere for DBS in depression. The closed-loop personalised approach rests on one published individual. The best sham-controlled trial we have is this year's Canadian study, and it found nothing in the blinded phase while its open-label extension produced two-thirds to three-quarters response. That's the state of play, honestly held.



Corn

It's a strange kind of progress. The field didn't answer "does it work." It dissolved the question into "for whom, at which tracts, measured how."



Hilbert

— and tuned, that's the part you're both circling. It's not the operation, it's the two years of appointments afterward.



Hilbert

I rang a man this afternoon while you were going on about the Canadian numbers. Met him on a train from Liège in oh eight, sat opposite me the whole way, right hand shaking so he couldn't fill in his crossword. Essential tremor, not depression. Had the implants done in Bristol. We exchanged addresses because he wanted the name of a glue I'd mentioned, and he rang me back about the glue, which is more than most people manage.



Hilbert

He told me the surgery was a Wednesday and he was home Friday. Then the work started. Eleven programming sessions over nineteen months. Eleven. Each one, a technician with a handset the size of a pocket calculator changes numbers, asks how he feels, sends him home for a fortnight to find out. He said the worst part was the half-second after they adjust it, a sensation like a coin dropping into water somewhere behind his eyes, and then nothing you can name.



Hilbert

Corn, you did forty minutes on whether it works and one line on the battery, which is the bit that actually recurs. His got replaced in a second surgery under local, he was awake and complaining throughout. Herman, keep your levels up, your left channel's dropped twice since the ultrasound fellow.



Hilbert

Anyway. He said the thing nobody prints: for the first four months he couldn't sign his name and it came back wrong. Better, but wrong. Looked like someone else's handwriting. He kept a sample in his wallet, both versions, to show people what the machine did. I asked him whether he'd do it again and he said he'd do it Tuesday. It's a Tuesday, so I expect he's somewhere doing it.



Corn

Nineteen months of tuning for a tremor, where the target's been settled for decades. Now imagine that tuning against a questionnaire.



Herman

That's actually the most sobering thing anyone's said today. The Parkinson's and tremor programming is hard enough — and the target's a motor circuit, you can watch the hand and adjust. In depression, the adjustment signal is the patient's self-report, weeks later. The biomarker work is precisely the attempt to swap that out for something you can read in real time.



Hilbert

The handset's the problem as well. He said the technician had three screens and a laminated card. Laminated. Nineteen months and the card was laminated.



Corn

The card being laminated suggests it was written more than once, which is more than can be said for some trial protocols.



Herman

I'll grant the programming burden, though the recording devices are the first real attempt at it — the Nature study's whole point was that the signal tracks recovery, so the handset gets a screen worth trusting. Eventually.



Corn

Eventually is carrying a lot of weight in this field.



Herman

It always has. That's the pattern of the whole twenty-year arc, isn't it — Mayberg's six patients, the crash, the connectomic rebuild, and every stage taking a decade longer than the people inside it expected. The twenty twenty-six critical review in Frontiers in



Herman (continued)

Psychiatry frames it as psychosurgery becoming circuit-based medicine — less an invasive surgical discipline, more a way of steering networks. I buy the framing. I'd just note that medicine became circuit-based the day it started measuring circuits instead of asking people how they felt on a scale of one to ten, and that day hasn't quite arrived.



Corn

Whereas Hilbert's man was measured in crosswords, signatures, and whether he'd do it on a Tuesday. Cheap instruments, honest readings.



Herman

The signature thing isn't trivial either — handwriting change after DBS is documented in the movement-disorder literature, and it's exactly the kind of objective, functional readout the depression field keeps saying it needs and doesn't have.



Corn

So here's where we land. The open question I'd watch is the simplest one: can anyone, anywhere, run a sham-controlled trial of subgenual cingulate DBS for depression that actually comes out positive? Because until that happens, the field is asking regulators and patients to accept two decades of open-label conviction and one remarkable closed-loop case of one — against a trial record that keeps saying no. And behind that, the race: ultrasound reaching the same tracts without a drill. If five people and a printed lens can do what two years of programming does, the surgeons are out of the loop.



Herman

The optimistic read is that this is one of the rare stories where both the sceptics and the believers have been right the whole time — the trials really did fail, and the mechanism really is probably sound. The error was thinking one coordinate could be everyone's cure.



Corn

Thanks as always to Hilbert Flumingtop at the desk, who fixed our levels mid-story and didn't ask for thanks.



Corn

For more along these lines, there's episode twenty-five twenty-seven, Do Brain Changes from Therapy or Pills Actually Last; episode eighteen, Beyond the GPU; and episode twenty-five twenty-nine, Depression Subtypes. This has been My Weird Prompts. If you found this worth your time, subscribe, tell a friend, and leave a review — it helps more than you know.



Herman

We'll be back soon. See you tomorrow, brother.

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