"Neuroimaging Advances for Depression" with Helen S. Mayberg

Transcript of Cerebrum Podcast

Guest: Helen S. Mayberg, M.D., is Professor of Psychiatry, Neurology and Radiology, and the Dorothy Fuqua Chair in psychiatric imaging and therapeutics at Emory University. Her research has characterized neural systems mediating major depression and its recovery, defined imaging-based illness subtypes to optimize treatment selection, and introduced the first use of deep brain stimulation for treatment resistant patients. She is a member of the National Academy of Medicine, the National Academy of Arts and Sciences, and the National Academy of Inventors, and has authored more than 200 publications, and participates in a wide variety of advisory and scientific activities across multiple fields in neuroscience.

Host: Bill Glovin serves as editor of *Cerebrum* and the *Cerebrum Anthology: Emerging Issues in Brain Science*. He is also executive editor of the Dana Press and *Brain in the News*. Prior to joining the Dana Foundation, Mr. Glovin was senior editor of *Rutgers Magazine* and editor of *Rutgers Focus*. He has served as managing editor of *New Jersey Success*, editor of *New Jersey Business* magazine, and as a staff writer at *The Record* newspaper in Hackensack, NJ. Mr. Glovin has won 20 writing awards from the Society of Professional Journalists of New Jersey and the Council for Advancement and Support of Education. He has a B.A. in Journalism from George Washington University.

Bill Glovin: Hello. I'm *Cerebrum* Editor Bill Glovin. Welcome to our monthly *Cerebrum* podcast. We are pleased to welcome into our Dana Foundation offices in New York City, Dr. Helen S. Mayberg, co-author of our most recent *Cerebrum* article, "Imaging Advances for Depression." You can find the article at dana.org.

First, a little about depression, which affects as many as 350 million people worldwide, and close to 20 million people in the US. Depression is treated through drugs and therapy. Unfortunately, antidepressants that were developed in the 1950s have gone on relatively unchanged for over 60 years. A new class of antidepressants called ketamine has shown promise, but there are still many questions surrounding it.

Dr. Mayberg is a behavioral neurologist who has an international reputation for her pioneering research to map the brain circuits implicated in depression. The reason we are able to talk face-to-face today is because she has recently re-located from Emory in Atlanta to New York City to become the founding director of the Center for Advance Circuit Therapeutics at Mt. Sinai, which is just a short subway ride from here.

We couldn't have a better guest to talk about depression. At Emory, Dr. Mayberg directed the Mayberg Depression Biometrics Lab, and was a professor of Psychiatry, Neurology, and Radiology, and held the Fuqua Chair in Psychiatric Imaging and Therapeutics. Dennis Charney, dean of the ICAHN School of Medicine and President of the Academic Affairs at Mt. Sinai, calls Dr. Mayberg "a spectacular recruit to

the Mt. Sinai health system." Eric Nestler, director of the School of Friedman Brain Institute and president of the Society for Neuroscience, says that "Dr. Mayberg's research team will help Mt. Sinai play a leading role globally in devising treatments for depression."

Welcome to the Big Apple, Helen. I noticed in your bio that you got a medical degree at USC but were a post-doctoral fellow at Hopkins in Baltimore, and also at the University of Toronto in the early 2000s. Among the many places you received training was the Neurological Institute at Columbia in New York. Then, there was your time at Emory in Atlanta. Where are you from originally? Has all this moving around been difficult?

Helen Mayberg: Well, it's wonderful to be here, Bill, and to be at the Dana Foundation, where I received some fabulous support in many of the locations I've been. Thank you for the opportunity. I'm originally from Southern California. I spent my formative years, including undergrad at UCLA, and medical school at USC, and internship at LA County Hospital before I moved to New York. I think my career has been nomadic. I like to say that, generally, I don't take sabbaticals, I move. That's been pretty much the story of my professional life. Now, I'm actually coming back to New York after, hard to even believe, 30 years.

It's not hard as much as I think it speaks to the idea that my career path has been to follow the science. We didn't even *do* imaging when I went to medical school. It was in its very basic stages. To get a CT scan when I was a medical student was to wait a month to see if your attending was actually correct with what the diagnosis was after the fact of what you decided to do.

Being in imaging and moving to places as the field evolved has been my modus operandi. I've intended to move as the questions have evolved, but the common theme has been that I've been interested in depression since my training in neurology. I went at the field not as a conventional course through psychiatry, but to think about behavior and abnormal mood as behavior, and how can you take a neurological approach to that problem.

I think each institution allowed me to work with a new set of people that saw it another way and enabled a group vision about how we might study this. Each place put a layer of sophistication, and different tweak, a different nuance, a different orientation. It's always hard to move because you hope you can get the spark from the new group of people. You hope that they'll work with you and see where you're going, like you look to see what they do. That's part of the decision of why you move to a place because you know that people there that are going to share your interest, and help you meet these objectives.

Bill Glovin: Right. That ruins my next question, which I was going to say: You are firmly established at Emory for a long time, and why you had moved to Mt. Sinai. Then, what do you hope to accomplish there? Maybe we could talk about what you hope to accomplish there, a part of it since you just answered the first part.

Helen Mayberg: I don't know if I get creative, just get the urge to move. I mean, I was at Emory a really long time, much longer than I've been anywhere else. The team was fabulous. The approach to think about moving to Sinai from, first, really, Dr. Nestler, and then Dr. Charney, was to realize the scientific and multidisciplinary strength of the institution. In neurosurgery, also the commitment to circuit modulation, Brian Kopell, the functional neurosurgeon there would be a critical partner, as Bob Gross was to me at Emory.

The issue now is how to think about all the pieces together. I've always kluged groups together. I'm a neurologist, but I live in a psychiatry department. I interact with neuroscientists or imaging people. I find expertise to address the goal. You're bringing engineers. You're bringing signal processors. You're bringing neuroscientists. You see what you can get out of people's study rodents. You read primate anatomy. It's always fitting it together toward the question.

What Sinai is enabling me to do is to embed the research together, so the behavior issues in Parkinson's patients who get brain stimulation will be studied right alongside the mood disorders and obsessive-compulsive disorder (OCD) when OCD patients are implanted. In our own work on depression, we'll study motor issues as potential metrics in the patient's web depression. With everything, I hopefully have learned from every previous opportunity, and work, and collaboration. We're going to work to see if we can have everybody co-localize, so we can all interact with each other in real time, in common space, and to do that together.

Really, we'll die trying. We'll have a good time, and get a part of it done, but the institution has basically said, that's new. Not that everyone doesn't always envision doing it, but getting neurology, psychiatry, radiology, neurosurgery, neuroscience; the pieces that all go to a given problem together will be what we'll attempt to do.

Bill Glovin: From a logistics standpoint, what's involved in moving a lab from one place to another? Does your research team come along with you? Do you build a new one? How does that work?

Helen Mayberg: In previous times, I've moved alone. I've never moved with anyone. I finish a chapter, evaluate if they're going to be the psychiatrist with the like-interest to work on depression because, as a neurologist, it'd be dangerous to be the one responsible for taking care of patients to map their brains. Does an institution have good imaging infrastructure and experts? It's like improvisational theater. You know your craft. Then, you work with other experts. You look to find the magic that makes a group work. You don't even know how it's going to turn out. You just know that this group of people together share a common interest. Then, we work to figure out how to make it work.

In leaving Atlanta, I will maintain an adjunct position at Emory because most of my team is staying. The work we've done and the patients we've operated on continue to be followed and managed. Our new NIH grants will be a combined effort between Sinai and Atlanta. Similarly, some engineers at Georgia Tech. We all need to figure out that logistic. In coming up here, I needed to see that there would be people that would be interested in what I want to do, and there are. There's a lot of interest from the movement disorder group, from neurosurgery, from psychiatry. Those pieces are aligned.

The technical aspects, I really hope to have familiarity. Actually, the first time in my life, I didn't feel like it's not a matter of not being confident, but that I wanted to see if the things that were just getting started at Emory could evolve. Ki Sueng Choi, engineer and imaging expert, will join and be a new assistant professor in Sinai. Allison Waters who's a psychologist, neuroscientist, and expert in EEG technology. She's been a postdoc, has set up this new component of the lab that we didn't do at all with EEG. This will be her first faculty position. The two of them will join me.

It was painful to take them from the team in Atlanta, but as both of their mentors, I can help to facilitate their career development, and take full advantage of their needed expertise to the vision we're trying to put together. I have two of my valued colleagues. I would have taken a psychiatrist too, but not

everyone can move. I would have loved to actually have other people from my team come here because of the more expansive thing we might be able to do with neuroscience, computational modeling, and expertise that Sinai has. We'll get by.

Bill Glovin: Sure. Sort of like a manager in baseball team who takes his first and third base coaches along with him to his new job.

Helen Mayberg: I will use that metaphor because you always want to leave town on good terms, maintain relationships, which I always have with every team, but not injure something that's working. It's narcissistic, but I believe that's true. I mean, I have resilience. I've got fabulous new people to collaborate with. There's an investment in, hopefully, the vision in me to make it work. I have every confidence. It will be different from Emory, but it will good. We'll move where we are taking advantage of things they do uniquely at Sinai that we don't do in Atlanta. That's what makes moves fabulous.

Bill Glovin: Cool. I think people get confused by the various imaging technology. Maybe we can begin by you helping explain what is available and what the purpose of each technology is. I know you could probably go on for an hour about that, but maybe we could sum it up briefly.

For example, this past week that leads to our Science Times was about a revolutionary new imaging technology called ORBEYE, a video microscope, which is being used by neurosurgeons at Lenox Hill Hospital to produce magnified, high-res 3D images of surgical sites on a 55-inch monitor. Apparently, you need these special glasses and darkness to see this, but it offers huge advantages over standard surgical microscopes and turns up maneuvering.

That's just something that just came along this week. I don't know if that has any implications in what you do, but maybe you could just give us a three or four-minute summary of how imaging has evolved.

Helen Mayberg: Imaging, I mean, just think about the word, it's how you see something. Have old=age eyes, and you get some little magnifiers. If you're in the operating room, you got to look at something small, you need a bigger magnifying glass. If things are moving around and moving in and out of focus, you need ways in which you can do that effectively if you're sitting with a scalpel in close proximity to a small space in the brain or in your abdomen.

The things this week about ways to look at an operating room filled with higher resolution to help do your job and see things that you couldn't see ordinarily will, I think, continue to advance. I know there are some interesting, similar kinds of technologies at Sinai, and very influential for how to be able to go to places in the brain that you might have been more reticent to cover. I think we're just going to see that with robots, with these specialized tools, that will be able to help people in ways that before would have been deemed too dangerous.

That's one kind of visualization. I think, scientific visualization is how do we get a visualization of something that isn't just strictly an enhancement what the eye does ordinarily, but actually pushing to a different way in which we look at a physiological process. From the pure visualization, when you think about the brain, unless you're a neurosurgeon, and you take off the skull, and you look at it, you have to wait until people are dead in order to actually see what's going on.

That's why a good neurologist can do an exam and know where something is happening in the brain because the brain is a wiring diagram, and everyone is fundamentally wired similarly. And when connections or areas are damaged, you know from pathology and the exam, where that is. You make inferences to take care of people. That's why x-ray CT was so fundamentally important in the '70s because, suddenly, you could see what you used to have to wait for at pathology.

An MRI, structural MRI, which everyone gets all the time, magnetic resonance imaging, doesn't use x-rays. It uses another principle. Same thing, I can see what is there, but because it isn't just a magnifying glass with better optics, it actually takes advantage of principles of magnetic fields, how different components of brain tissue respond differently to magnetic pulses, clever engineering, and physics. Suddenly, you can start to get surrogate signals of other aspects of the brain that you can't see, or you can't see without taking the brain out and staining it.

You can develop ways in which you can see the difference between white matter and gray matter. We're watching the evolution of studying people with CTE or with traumatic brain injury where you used to not be able to see anything. Suddenly, you can see things with special sequences. We can, instead of injecting a dye, and taking an x-ray and an angiogram, now, you can just do special sequences, and watch blood flow in the brain or an MRI. Safer, faster, easier, can superimpose images. You can take advantage of imaging science, computer science, and look at combined measures.

The other thing about imaging, where if you think about it is visualized physiology, are things that you can do with things like positron emission tomography, where you can inject a radio trace or understand the chemical principle, put a radioactive tag, and get a little beacon that gives off activity. By understanding the physiology, you can look at a map at the brain in action. We can look at a map of the brain's chemical receptors, or you can look at what happens when you challenge the brain, and you can watch systems change.

There almost becomes an infinite way that you can exploit these various technologies, depending on what you want to know. Instead of it just well, "I just want to know where," you can know what and how. You can add a layer of the anatomy. Just the activity of brain areas talking to each other, the chemistry, the resting state, the response to physiology. You suddenly have a multimodal view of the brain in action.

All of them requires specialized ways to look at the brain. That's not even including the real gold standard, which is true physiology. What's the unit recording of the brain? What's a cell's action potential? Put on a little electrode, a little wire, and listen to a cell responding. A cell that responds to a house versus face, two different faces. Learning and piecing together painstakingly cell-by-cell how we're wired.

We're in this evolution of various levels of resolution that you can do with the cellular level to the human level. You can do it in humans with the brain open in an operating room, with electrodes implanted as people do with epilepsy patients, and map them while they're in the hospital, to scans that let you look at different features with different experiments to waiting until someone dies to look at things at the microscopic level.

Bill Glovin: A microscopy, for example, two-photon microscopy, we did a story on that. That seemed, even though it wasn't being utilized in human beings yet, it seemed like it had an enormous potential. I think the dye that you mentioned might be associated with that.

Helen Mayberg: Similarly, optogenetics has revolutionized, as one technology dreads, another technology with chemical mapping. As we've understand the brain different, people are always going to have a better mousetrap of a cleverer way to exploit chemistry and physics. That's the beauty of supporting large-scale neuroscience for its own sake, not only as an application. That we accept me as just poor man's imager. It may not utilize technology that I can do safely in humans.

Another brain doesn't need to be open even though, obviously, with the brain stimulation, we have an entrée into the brain in one small place, and we're to take full advantage of that. We have to read veraciously what's done in a rodent with a methodology because even if I can't take advantage of the technology itself, a person who's not a mouse, on the other hand, how cells communicate the basic physiological principles are the same in mammals.

How do we exploit how cells are organized, talk to each other? What is systems-drawn science? How do we move from a cell to a dish with cells, to a mouse, to a nonhuman primate? What can we learn that, then, we can take the part that we can translate into people, knowing we can never do what you can do in the other animal model systems? This is one of my big hopes at Sinai, is how do we go by directionally with our translational science, not just the usual model. Humans will wait for everyone to scale up what we know from small animals. To actually say, "No, that needs to happen all the time," but at the human level, let me tell you the question, if you could answer this for me, what a difference you could make, the reverse translation.

I know the circuit in humans. I've got an electrode in it. I've got an imaging map of what it's connected to. I can know the difference between when someone gets better or not. I know the PET scan signal. I know the EEG signal. I really don't know how it's working. Can you set that model up for me? It'd be really great if we could do it in a monkey because that's got a brain like a human. That maybe hard but I've got to know the anatomy in a mouse that's closest to the anatomy in the human. I'm missing some pieces in the mouse.

I don't know what a guilty mouse is. I don't know what a suicidal mouse is. I have to care about that in patients, but I can understand the dynamics. I can do calcium imaging. I can do optogenetics. Like a Chinese restaurant menu, "Can I have this please? Can you use your best methods to help me understand how this system might be working?" All makes some inferences to the people but try to be in my neighborhood in the brain that we need for depression. Don't go just into a neighborhood that's easy because that's where you are. How do we get that dialogue happening, so that our work is informing the basic science, and the basic science is informing us more directly?

Bill Glovin: In terms of brain stimulation, which you mentioned, maybe you can talk a little about how that works with imaging. Also, you mentioned Brian Koppel who's a deep brain-stim pioneer, and the Mt. Sinai press release said that you were expected to partner with him, and you reiterated that sentiment earlier. What can you learn from one another?

Helen Mayberg: First of all, I can't do anything that I do in the brain stimulation space. I'm not certain. Again, what you learn is your ideas or your own ideas that you have in your own head, unless you can

get other people to actually think you have an idea that's worth partnering on. Just as I was able to do with Andres Lozano in Toronto for our initial studies, and then with Bob Gross at Emory, a skilled surgeon is essential to any new idea in brain stimulation. They're the masters. Having a surgeon that has good hands, who has a good mind, who is a good partner scientifically, but who takes care of patients and is a skilled surgeon is essential.

Brian, as a functional neurosurgeon, thinks widely and broadly about these questions. He's a well-regarded Parkinson's DBS surgeon. He has worked and collaborated with many on cortical stim that ended up not being pursued for depression. He has a long interest in depression itself, which makes my collaborating with him and having him be the surgeon particularly exciting to me personally. He has a strong, dynamic practice in functional neurosurgery, and takes care of patients with Parkinson's, and tremor, and OCD. He's going to be my primary collaborator to help build this center. He runs a big clinical group already, but it does research independently.

His partner, the movement disorder people, have research that may or may not interact with him. The OCD experts are in psychiatry. They utilize him. They have an interaction with him. He's the focus, but the work that goes on with Parkinson's doesn't inform directly the work that goes on with OCD or depression. What we're trying to do is really see how to build the research unit, so that Parkinson's behavioral problems are informed by what we know about OCD. These Parkinson's patients who get DBS surgery, they have OCD. Many of them have depression. How do we start to think about a new intervention for depression and Parkinson's based on what we know about studying depression itself with our DBS approach?

Again, he's in a central role. I would never have moved to Sinai without knowing that the functional neurosurgeons ... It's not just Brian. There are other neurosurgeons, Saadi Ghatan in epilepsy group, and others that I haven't even met yet. Knowing my point person since Brian is the main DBS surgeon is going to be ground zero for the collaboration.

Bill Glovin: Kay Jamison, who's one of my *Cerebrum* advisors, really liked the article, but said she was disappointed at the lack of positive findings in terms of, I guess, advances in imaging. Do you get frustrated with that, or do you feel like we've come far along, or…?

Helen Mayberg: I'm working on the glass half full rather than glass half empty, even though I think good sciences, you're only as good as your last paper. You have to always assume that you've missed something. I think, maybe the negativity issue responded to is the first part. I think that what Dr. Dunlop, Boadie Dunlop, my important collaborator on these imaging and predicted biomarker studies, emphasized in the piece was that everybody over the last 10 years with the advent of a human genome project, and having the gene map done, it's going to be really straightforward once we get the genes that will really dial in variability, and we'll understand it all.

Well, without the alphabet, that doesn't mean you wrote *War and Peace*. Trying to figure out where the signal is and where the noise is, is partly what question to ask. I think we continue and have as we become very technology-bound, there's a new toy, and we look to exploit the new method, and the question is toward what question.

I think in psychiatry, the holy grail is how do we make these diagnoses not be syndromes, and we make them diseases. The definition is a disease versus a disorder is you have pathology. It's Parkinson's

disease, Alzheimer's disease. It's bipolar disorder. It's major depressive disorder, excessive impulsive disorder. It's not by choice. That's by definition. We don't know the pathology in disorders.

We're looking for surrogates, taking a drop of blood or a sample off the cheek to be able to relatively and extensively now map your genome. It doesn't necessarily get you close to the syndrome as a unifying concept. This is why people have said you can have a diagnosis of a syndrome but have varying combinations of symptoms. Maybe we should classify people by the kind of symptoms they have, and it will be clearer.

We learned in neurology long ago that, like in Parkinson's, not everybody has tremor, even though tremor is a defining symptom in many patients. You can still get pathology in Parkinson's disease, have more rigidity, and gait problems, and may not have much tremor. We don't give it a new name because with the end, we can go pathology.

Psychiatry has still been struggling with what's the right way to characterize these syndromes where people suffer, and we need to give them some kind of name in order to take care of them. We luckily have many treatments. Then, our problem is that we become frustrated by the fact that treatments don't consistently work for everyone even when they seem to have the same syndromal features. We're trying to use imaging or use genetics. It hasn't worked.

Kay may be frustrated by the positives. I would argue. I think we've asked the question that we've approached outcomes as being uni-dimensional. As different kinds of treatment, just like imaging people, everyone advocates for their method. Now, you use a method that works to answer the question you have. If you are a therapist, you want to protect your own interest. You look at the world through the lens of what you do, and you look for where you can be helpful.

If you're a psychopharmacologist, you have a bag of many chemical treatments. You look at the world, and say, "Well, if drug A doesn't work, drug B clearly may." I can go through an algorithm in my own mind because my goal is to get a given patient well, but it's trial and error. I think that we are frustrated by the fact that we have many treatments that work. That's not an indictment of the pharmaceutical industry. They've developed treatments that meet the bar to get, on average, people well.

The problem is and the blogosphere in the world now is if that didn't work for me, it may sit bad. No, if it didn't work for you, it wasn't for you, any more than they gave everybody with an infection penicillin, and you had tuberculosis, or you had a non-gram-positive organism. It's not going to work for you. Does that mean penicillin is a bad antibiotic? No, but it's a specific antibiotic, and we have to have an approach to precision psychiatry in the same way that cancer does; infectious disease does.

Infectious disease has done it for -- I'm probably underestimating -- a hundred years since the beginning of penicillin and every antibiotic developed something new. We can grow out the organism. You've got the infection. You pee in a cup. You cough in a cup. We stick it on an agar plate. We grow it. We make sure we grow it in the proper environment to find weird organisms. Then, we test different treatments on the plate. Then, we say, "Oh boy, I looked on it at the microscope, and it should have responded to penicillin. It's resistant." We got a drug for that. We give you what you need. Why? Because if we don't give you the right drug, you're going to sicker and you might die.

Cancer, everybody dies if you don't treat them with the right thing. Now, we got markers. You take a tumor out. Yes, someone looks at it, and someone types it, a gene, a receptor. Now, we give you a drug that's good for that. We talk about it nonchalantly. It turns out brain tumors have got markers that we thought only belonged in the gut. I mean, the whole world has changed through these precision metrics. We're surprised when we don't even have a disease. We've got a syndrome. We're looking at the wrong thing too soon. I know the genes are going to help, but we're going to need to filter the brain into types before we look for the gene marker because it's too noisy.

People have been looking for the gene marker. It's not working. (A), everyone is impatient. I'm impatient. I think it's reflected how we ask the questions, so that we are efficient. We've got to always be trying to reduce noise. We have to be like neurologists and find the patterns. Let's celebrate individual differences. That's what psychiatry does. Everyone's got a narrative. Everyone's got a narrative for cancer for that. Right now, I just need to know what your type is. Then, I'll deal with you as a person.

I think the imaging, what I'm most proud of the work at Emory is to actually ask the same question that I asked in Texas. We got our first scans of ... It wasn't the first group of scans, but we did a group of patients, did PET scans. We saw another pattern of unipolar depressed patients, but we knew that this group of people because my team was also taking care of them. Some people have gotten treated by the doctors and got better. Some didn't.

We simply said, "Well, let's go back to the scans." We went back to the charts and said, "Tell me who got better and who didn't. That's all I want to know." They all got treated with different drugs, different things. Went back to the baseline scan and said, "They started in this pattern, and the frontal lobe was the same in everybody." If I analyze it again and said, "Eventual responders and eventual non-responders." We saw the signal in area brain, the cingulate. Cingulate was overactive in the people that did great eventually, and underactive in the people who didn't. That one experiment, we published in 1997, *Neuroreport*, 18 people. It was fundamental and something I followed now to two institutions.

When I moved to Toronto, we looked at it again. The same thing controlling for a drug. We studied the puzzle. Then, we started to look at how does a brain change on cognitive therapy. Then, said, "What's the difference between cognitive therapy and drug?" We didn't ask the question right in Toronto. We got that we knew that the brain changed differently to the two treatments. Not surprising if they had redundant changes with successful treatment. Why do you need both of them in a complementary way? They changed the brain differently. We said, "Well, if the brain changes differently going from sick to well with two very good treatments but with likely different mechanisms, maybe the brain started differently, and we shouldn't assume a final common pathway for anything."

I got to Atlanta. We set up our new studies with Boadie Dunlop and Ed Craighead. We said, "We're going to compare drug and therapy." Why? They are the bedrock of how you start when you treat people. Look, I spend a lot of my time, and people respond to nothing. We end up operating on their brain, but those people started with a regular depression. They responded to the treatments that they got. They had a malignant transformation and converted to another state.

The research is going in two directions. One is, let's go back to fundamentals. Let's take people that would be willing to take drug or therapy, never been treated with anything in one experiment. People who have been treated in the past or coming back with a recurring episode. While we use fMRI for one

experiment and PET scans for the other, that's the least important part. The idea was we're going to scan people. We're going to randomize them to one treatment or the other. We're going to give the best expert treatment by two expert teams.

At the end of three months, with this kind of treatment, you're coming in every week. You are either well, which is what we all hope to get, and you should get with the treatment. That should be your goal, or actually that treatment had very little effect on you over the course of three months. I don't want to get into I'll take anything. I'm looking for a biomarker that tells me win or lose.

People went crazy with that logic. They've said, "You're cherry picking." Yeah, you bet we're cherry picking. I'm looking for a biomarker. I want to know unambiguously if from your scan pattern at the beginning, I'll get you well with a treatment or you categorically fail. I want to know it before you bother to spend three months of your time, but we added a tweak to it and said, "Let's ask the brain. Maybe the pattern is the same brain areas because we've been seeing a circuit in the brain a long time. Let's look at the pattern, and ask the brain statistically, are there brain areas that show the opposite pattern if you do great with drug but failed therapy?" That's one pattern implying that if you failed therapy, you really have the drug type.

Alternatively, if you did great on therapy, it's the same pattern as that failed drug. It could be that it's really independent patterns. That statistical analysis would never work. That was setting up the prior statistically to ask a question that nobody, in my mind, because people told me they felt that was like, "Why would you do it that way?" Well, because when you listen, I don't have a harness in the game. I'm not a therapist, and I'm a psycho pharmacologist. I listen to them going, "Why are you arguing with each other about who's best? You're both right, not at the same time," but maybe because the community believes you can get better on one or the other. Let's test it out, and we'll hit all these things even though what I really care about is the brain type.

What we found is that there were brain areas that could be in an up state or a down state. The state they were in predicted that you would get better or not to one treatment, as well as to the opposing treatment. That's step one. You say, "Well, that's fantastic, interesting," whatever adjective you want, but, now, I want to know if your brain scan, you failed the treatment I gave you and it said, "Well, you really had the other type." Well, how do I prove that you really have the other type? Well, I gave you the other treatment.

What we did in this experiment also, which was the brilliance of the team is, yeah, we really care and control for that first three months. If you're partly well, I'm not going to take you off of the drug you're on. I can never have a pure experiment for the people who got partly well on drug. If you've got therapy, and you got partly better, I can't really undo what you learned in therapy. I'm stuck with the fact, whatever you got, if you've got anything, question is, am I going to add the other treatment? If you really should be treated by brain type, we would predict that you will remit. You'll get totally well when I add the treatment that your brain said you needed from the first half of the experiment. That was true.

It particularly worked for people who needed to have therapy because the third level of the experiment found that if you had the drug type, you could actually be a dual failure. That one drug, escitalopram (Lexapro), very standard serotonin reuptake inhibitor first line treatment might not be the drug for you, but therapy wasn't for you either. Then, we look at the subset of people who failed both compared to people who could get better on one or both.

We're back to the beginning and say, "Can I predict people who are going to have trouble?" It turned out those people had an abnormality. Well, they don't have an abnormality. They had overactivity of the very area that we target with brain stimulation. Their sadness center, their area 25, was overactive compared to people that recovered from these two standard treatments.

I believe that the beauty of that small experiment built on 20 years of thinking about brain types but set it up to look at it in a slightly different way, kind of the United Nations in some way. I've learned over many years you can't fight City Hall, that there are magical thoughts in psychiatry. People think they know. I have been told more times than I can tell you, "That idea, stupid idea. It doesn't work that way. You are wrong." I've learned to just listen, go back to the lab, and prove it because only data changes dogma.

You have to, then, once you get an experiment, and have a new founding, it forces people to see it a slightly different way. Will people allow themselves to move in another direction? Then, over time, where in the beginning maybe don't believe it, pretty soon, it's like, "Yeah, that's obvious." Then, after a while, other people are doing it. Whose idea it was, it doesn't matter because, in fact, the idea is we are habit-driven. We need to get people well. If trial and error is what we've got, you better hope that your doctor does that trial and error and doesn't give up after two. That's what I care about.

In the meantime, well, people are doing the hard work in the field of that taking care of patients. My job is to try to figure out how can we turn it on its head. How can we look at these observations slight different with the data? When we did it with fMRI, we had to take a different computational approach, and said, "This area 25, area in the cingulate, it's the center of my universe, but it's a center of the depression universe." I want to know how the brain, if it's overactive in the PET scans, I'm going to use it as my anchor in the fMRI scans and say how the drug and therapy responders look differently in a circuit that centers on area 25. What's the connectivity? Not the whole brand could have set it up in a much more elaborate way.

Then, I'm going to go for something I can understand more simply. How is 25 talking to the rest of the brain differently in people who get better or don't with drug or therapy. I hit two birds with one stone. If this area 25 really isn't important to the argument, the experiment will blow up. It won't work in the statistics. Well, it turned out there were three areas that if you're connected to area 25 ... The pattern on the fMRI of the crosstalk between these three areas is positive. They're connected. They're communicating. You do great on therapy, and terrible on drug. If they're disconnected, if they're not talking to each other, functional connectivity is low.

Bill Glovin: Can I just interrupt for a second? You're mentioning this area 25, this Brodmann area, which you were the first to identify. I think for our listeners they might not understand what you're actually referring to. There is an area in the brain. Does it light up for depression?

Helen Mayberg: Area 25, it's actually a shorthand for Brodmann area 25, which is a designation by an anatomist at the turn of the last century who looked microscopically and gave a numerical designation for all cortical areas. In the cingulate, a deep part of the brain, a C-shaped structure below the frontal lobe, part of the limbic cortex, part of it is numbered area 25.

And that region, over the last 20 years, has shown up in my team's experiments, but other team's experiments. We became perhaps a little fixated on it, but I didn't discover it, but that we made the

observation that area 25 was very important for the effect of antidepressant, successful antidepressant treatment that when you treated people with Prozac, with Fluoxetine, the frontal cortex, which have been underactive, normalized, increased its activity on a PET scan.

What we saw is that area 25 decreased its activity. We haven't seen that before. It hadn't been described. We next did an experiment. It actually was funded by the Dana Foundation, one of my first grants. We provoked with a personal sad memory what changed in the brain when people went from neutral mood to sad mood. We knew that sad in a healthy person who might recollect a time of loss. Most people use loss of a family member as what they chose to remember. We wanted to capture the negative mood of depression, not the cognitive part.

We induced a group of women to think about something intensely sad to feel it, not just think it. We mapped in real time with a PET scan, blood flow scan. We were hoping to separate the frontal cortex from area 25. What we got was that area 25, the same part of the cingulate, was the most activated area. It just cranked up its blood flow. There were some other areas like the insula, which all come back to in a second, all part of the limbic, how you feel emotion is what they do, and we turn the frontal lobes off.

We have this first observation that you could not separate the emotion part of the brain, the sadness from the thinking part of the brain, the frontal cortex, because while depressed people, when they get into that state, they can't think straight. When healthy people get sad, you tragically turned inside to yourself, and you don't think about other things outside yourself either. You get lost temporarily. Then, you realize, you're walking down the street, get hit by a car. Your frontal lobe comes back on, and your mood goes down, and goes away.

That was the important part of that observation that the frontal lobe in area 25 were toggled. This area 25, that's why it became such an important area, is in those early experiments on Prozac, on Fluoxetine, and then on Paxil, then on Venlafaxine, every experiment we did with SSRIs, if you down-regulated area 25, you got better. If it failed to turn down its activity, you did not get better. We have this clue that some people get better, some people don't. We were chasing the mechanism of how you are covered.

The change pattern, a biomarker, a prediction is about something about the starting place. We were trying to take what we knew about the change to almost imagine what might be the starting place, but, then, let the data tell us what it was. In the PET scan study I described, we have an upstate and a downstate. It wasn't about the cingulate. That turned down to be something important but not at our level of analysis. What ended up being the biomarker we're now testing prospectively to see if it works was the insula.

The insula was the area we also noticed that are mood induction, our depression treatment studies, it changed with treatment, and it changed in concert with area 25. Its activity at baseline, high in selectivity drug type, low in selectivity, therapy type. 25 seems to be more of a ring leader. When it gets stuck ... It can be up, and the insula can do its thing, go up or down, be regulated by treatment. When area 25 seems to be stuck up, that may be an indicator of you're going to have trouble.

It turned out, dot, dot, dot, getting to the patients we operated on, who don't respond to drug, like all of them don't respond to therapy, don't respond to ECT or electroconvulsive therapy, or TMS magnetic therapy, people who are not responding to anything, they had, at baseline, overactive 25. We thought

we could insert the electrode. At the time, the way that area 25 worked, was that it blocked activity. Won't we want it to go to decrease its activity? We can't regulate it, but the other way sold it. Put the electrode in, and we'll do it directly. It turns out it probably doesn't work that way. It's about its connections to other areas.

We're back to ... You can see. I mean, not trying to either confuse you, confuse myself, confuse your listeners, but, in fact, there's a continuum of experiments. It's a network of brain areas. We study it and we define it with one kind of imaging, one kind of experiment. We believe what we've got. We do another experiment. We go, "That one doesn't seem to be working, but, gee, these other areas are there." You're iteratively figuring out what are necessary and sufficient brain areas.

How are they wired? Talk to the monkey people. Talk to the rodent people. See what the optogenetics people are doing. Have a white matter map. See how they're connected. You start over years building up the map, building up the circuit, testing how pieces of the circuit work. DBS experiment was the ultimate experiment of causation. Here's the state of the network. I'm going in. I got a surgeon that can go precisely where we want. Let's see if it works. Then, we go back and say, "Okay, let's go back to our less sick people, and test this circuit also."

Not only is it bidirectional translation between humans and basic scientists. It's bidirectional translation between patients who are having their first episode of depression and having their fourth, where they're not getting well. Those patients have to be informed by our studies right out of the block. It's the same circuit in different states. It's telling us that maybe these circuits are breaking down over the course of a depressed person's life in a way.

Like multiple sclerosis, some multiple sclerosis patients have an episode where they have an event, and they get neurological symptoms. Then, they get treated, and it goes away. Some don't have many episodes. Some have an episode, and they always get mostly better. Some people have this progressive course. It's about the white matter in the brain keeps taking hits. As you get a hit in the white matter, that's framed connections in the brain. You're damaging random circuits.

We're taking the same approach to depression, except it's not a random hit in the brain. We're saying, "This circuit seems to be vulnerable, probably genetically vulnerable." We're seeing that in people of therapy, the circuit is mostly intact. We can just train it. It is weak. People who need drug, parts of it are still adaptive, but parts of it are breaking down. We can fix that. By the time you get to where you're feeling shock therapy, we look at our circuit and go, "Wow. With different kinds of imaging, it's breaking down in different ways."

To me, people go, "Nice. You're working with surgeons." No, I'm working with psychotherapists too. It's all a continuum. The therapists have to know what the surgeons are doing. You're going to have to deal with it because once we fix the brain with Brian, or with Bob, or with Andres, the surgeons, their part is done. Now, we've got to retrain the circuit. I need a therapist. I may need some drugs.

Everybody's got to see that no one way is it, but it's all part of the whole. All these pieces, all these teams, has just reinforced that you need multiple ways to approach this problem, and the types is to me, the fundamental starting point.

Bill Glovin: In the Mt. Sinai press release, you actually said the aim is to catalyze a clinical and scientific culture shift. That seems in line with that whole idea of culture shift.

Helen Mayberg: I'm working on the term "culture shift." I think this is everyone in clinical neuroscience getting back to their roots of why we all went into this. Everybody was fascinated with and perplexed by how this complex behavior work. Neurologists think about patterns. Neurologists says as a culture in medicine, work on order. Psychiatry works on a gestalt and has had chemistry as its work horse. We all are looking for an integrative approach, and how do we come to work on it together. It needs some different catalytic energy because we are compartmentalized in camps.

Now, Guy McKhann, my chair of neurology when I was at Hopkins, and medical director at the Dana Foundation, has always been an advocate for, how does neurology and psychiatry come back together? We have these artificial divides. I mean, I say I'm a behavioral neurologist only to make it very clear I have to training in psychiatry. My whole life has been about depression. I'm the first one to say I am not a psychiatrist. On the other hand, I'm not a neuropsychiatrist either. There are people saying, "I'm interested in psychiatric problems in neurological patients or behavior." We put labels on ourselves, which put us into camps in which we need to be together and aren't apart.

To me, the culture shift at all attempt to lead is how, "Look, call yourself whatever you want to call yourself. Give yourself a brand, but we're going to do it because the patients cannot separate. They need all of us to be working on their problem." That, to me, I think is just changing the organizational structure, and enabling the collisions of different kinds of expertise to come together at the same time. It's the same problem. We'll eventually get it together.

Freud was a neurologist. In the 1700s and 1800s, all of the ... I mean, Wernicke, Broca, all the people we think of as the leaders of the revolution in neurology in France. What they wanted to know was what was schizophrenia. They were trying to study the hardest problems, Alzheimer's. They got lucky on certain things. They were frustrated like Kay Jamison was. Why can't I see it in the brain?

Bill Glovin: Sure. When you see all these terrible stats about depression, and the economic ramifications of it, and the suicidal, and suicide rates go up, I mean, as somebody who's been in the field monitoring it all these years, is it a problem? Are we just basically realizing that because of the way we report data that we're identifying it better? Do you see progress, basically ... Or is it a problem that's getting worse because of social media and all these other things? I mean, yeah.

Helen Mayberg: I think that, fundamentally, there is a science part, which I do. I'm neither a politician. You're an advocate for your patients, for your science. That's a whole other discussion. I think that it's important to separate where the tools we have can get at the problem, so we're scientifically in an infancy, and that we have to ask the right question, and use the right tools. Problem one.

Depression, I think the good news and a positive spin on the terrible stats is the fact that people are way more comfortable about talking about being depressed, which means they have much more of an opportunity to be treated. The takeaway is we have treatments that work, and we have experts in many fields that can take care of people, and there are options for people. The fact that we talked about it openly is the first step. I think we are confronted because of our communication environment now, with everybody talking about it. That's a good thing.

I think, by not having a biological definition, depression as a word ... Again, so funny how things come together. Bill Safire getting around the Dana Foundation, the master of the study of words in culture. Depression is the worst possible word for what I study and what I do. It happens to be the one. It's hijacked. It is the word we use. If I could come up with a biological way for the drug, and therapy, and resistant type, and to remove that word from the lexicon, it couldn't be fast enough because the word ...

It's like schizophrenia. A healthy person who changes their mind is not schizophrenic, any more than a person who is sad because they broke their $100 manicure, which probably costs more now that I'm in New York, but that your disappointment, lose your job, have a bad day, we use the word "depression" as hyperbole. We also use it for normal stress, and that we don't know because of its common use. I don't think it's getting worse. The numbers on epidemiologically, the prevalence and incidence, it's the same. It hangs around 10 percent of people will get a depressive episode at some point in their life. It's a very common problem.

Thus, the culture. Thus, the environment. Is there something about how we live increasing that? Time will tell. Stressful lives are not a good thing. Many people write about it. If you have the wrong genes with a stressful environment, you may be a real setup. However, the notion of the word is the problem in getting a treatment they need is essential. The problem is this, we have recognized through these experiments is there's a group of people that will not get well if they do not get therapy. That's what they need.

Tuberculosis, you will not get well with penicillin. Not only are you going to have progression of your tuberculosis, you're going to get other people sick around you. They will be cotangent. There we go. It is essential from these kinds of early data to recognize that we need to offer people treatments for what they need. I don't see people not giving people the cancer treatment they need because it's not in your health plan.

Our problem now is healthcare delivery that's evidence-based. Someone takes an evidence-based stat at the lexicon in certain fields. We are evidence-based. That's how we get drugs approved. It's not willy-nilly. We look to see if, on average, it works. We have treatments that work. People don't have access because the dogma says, "Well, these drugs will work, and so therapy is expensive," or people say, "Therapy takes time. I don't want to take the time. I don't want to get into it with some of it. Just give me a pill. I'm in a hurry." No, you get the treatment that is what your brain needs.

Then, I have people say, "Well, it's not like we're going to do a scan to decide how to treat people." I never heard of cardiologist say, "I think you're having a heart attack. Well, yeah, I can see it on the EKG. You got chest pain. I think you don't get an angiogram." You want to look at stigma. We got to look at ourselves, and how we have health policy that does this.

I think the next layer of that part of the work is to say, "There may not just be that you're sick a little longer, and that has financial consequences. That may have damaging consequences to your brain." Getting drug that you don't need, it's not benign. Getting therapy that you don't need, well, it's expensive. Actually, you may shape your behavior in a way that isn't particularly good for you either. We need to see these treatments as they are affecting our brain. They are, hopefully, making it better. If they're not, they are having consequences we don't even know how to deal with that.

Right now, from our studies in Emory, you never want to go, "Well, you go replicate it." Well, one experiment, the PET scan, we're treating, we're doing the scan, we're treating by brain type to see if it works better than flipping a coin. Look, we learned a lot about biology. We may not want to implement it in the clinic, but we're testing it. We have an NIH grant. Right now, based on the numbers from the fMRI study that, in essence, replicate what we saw with the PET scan. Right now, my medical advocacy says, "You don't need a scan."

A patient who goes and get help, you takes a test online about, "Are you depressed by current clinical things?" Go to your doctor. Go to your GP. Your GP is likely going to start you on a medicine. Take what they take for three months. Do exactly what they say. If at the end of three months, you aren't in remission, ask your family doctor not to give you the next drug or to refer you to a psychopharm, send you to therapy, and invest in getting psychotherapy.

If you decide, "I'm going to a social worker. I'm going to therapy. I'm going to do mindfulness," whatever you decide in that route, you give it three months. When someone says, "No. I think you just change therapy or just do it longer," go, "No, I want a referral to take a pill," that if patients use the findings of the data that if you didn't get matched to the treatment that would have matched your brain type, but that you would get better if you got the alternative treatment. You would only go through two treatments, and you would have, at least, in our data, we picked up 80 percent of the group.

You still could be that 10 percent that isn't going to respond to the combination of our first line treatment. Then, you get a referral to psychopharm. But to deny people who may do best on psychotherapy because they enter the clinic at drug. That's going to be the way we tend to do things, would not have learned anything from what we learned from the experiment.

I think that that we can be pragmatist in the clinic, informed by the experiments without implementing the extra, the lab test, if you will, because it's not ready for primetime, but the logic is implementable now.

Bill Glovin: Before, when I mentioned that video microscope, the ORBEYE, in the *Times* piece, it was talking about how the cost is from $200,000 to a million dollars. There was nothing in your *Cerebrum* article about the cost of imaging equipment. Does that detract from use? Is the price coming down as more companies enter the market? Are you getting enough funding? I mean, the whole business climate around this, I'm sure it's something you always have to be concerned with.

Helen Mayberg: At my level, I live in an ivory tower. Right now, I don't worry about three steps down, will anybody use it? I want to develop methods that are precise, robust, and do what we claim. The implementation at the clinic side is the next step. It's not that I don't think about it. It's a big issue because scans cost money. That's always going to be the pushback. It's an added cost. Again, I may be snappy or not so snappy defensive retort. The cost of an angiogram is not a nickel.

The issue is: fMRI scans of the type we do, we pay by the hour. That's a research cost. I think my costs are going up now that I'm in New York City. I budget that into my NIH grants, we all do, or any grants that there's a cost, people don't want to lie in a scanner longer than an hour. We looked to be judicious with time. We're talking about, the scan we do is the six-minute scan. If we also do a structural scan or might have reason to develop methods with white matter scans, I don't want to miss an opportunity to get everything all at one time experimentally.

The part that I'm talking about that we use in these papers, these six minutes, let's say 12 minutes, because we get the anatomy also. PET scan costs more. You got to make the tracer. It's a radioactive tracer, which means it decays. You've got to bind the tracer. It has to get there in due time. Those scans cost more. They're more on the order on our research scan of $1,500, $1,700. Anybody listening to this who's had a clinical MRI scan done in the clinic knows that it's not a $500 or $700 procedure.

In fact, just like I can be an advocate of that we should use test, and it has to make a big difference that we don't have something cheaper and equally effective, then we also have to consider what could be cost containment going forward. I'd like to think that by doing a research, if we believe our brain types, we can then reverse engineer to look for a surrogate. I have had people say, "Well, what we need is a bedside test, and you do it in the lab." That hasn't worked; clinical science and symptoms. If the brain scan findings, if these different methods are replicating, then we use the brain types to work backwards to look for a clinical or a blood-test metric. That would be a game changer.

We've been starting to explore with our group in Atlanta and a colleague in Munich where we've said, "Let's look to see if there are genes that track with our brain type," because we don't have big enough samples. You need tens of thousands of patients, which certainly Sinai does, the Broad does. There are huge consortiums in the world to look at people with diagnosis, and have the genetic material, and search for genes.

Then, psychiatry, schizophrenia, depression, bipolar share a lot of genes. That's not helping me for treatment yet. But we took our insula marker or fMRI marker and said, "Let's filter your brain type on the gene." Take one study, and look for, "Is there a gene marker of that? How does that may not see any genes that go with the brain signal?" because the brain signal has different strengths. You have an activity measuring the brain that's above a threshold for us to make a decision, but it's a continuum of values.

You run it and the genetic profiling analysis. It turns out there are some correlations between the brain type and certain combination of genes. Then, you take those gene types and you say, "Let me test it against another group of people." For us, it's the other group of people with the other scans. Can it alone? Can the PET scan-derived gene type predict the outcome and the people who had the fMRI outcome? Some interesting clues not yet ready for primetime.

The logic is, to me, what's important that everybody wants a gene because you could do a swab, and you could get any answer, and the cost of that has gone from unmeasurable to under $1,000 for a gene. I mean, you can get certain things with something you can buy as a gift. Send your swabs off on to those commercial outfits. The research grade work is still expensive, but you don't need 50,000 people to do what we did. The naysayers, they say, "I don't believe that." Well, take our genes, and run them in your big profile. Let's see if they show up, because when you look at what the genes code for, they're coding for cells that have been implicated in depression through studies in mice.

You've got to be patient. It's like a big puzzle where you start to put the pieces. You don't even have picture on the box, or even know what you're chasing. You can start to get a cluster of pieces together. You pick up another random piece. It's not necessarily within a fit right there this time. You'll throw it out. You, at least, to have to assume it should be on the table and put it down. You just keep looking for these points of intersection. They start to show up.

Once you get a hit, you got to start reeling in. It's fishing. You can't go on a ... This is war against a disease. I'm not going to apologize for, "You're over mining your data." I'll deal with that when we're ready to publish, when we're making an argument of an experiment. You have to have rigor. When you're trying to figure out how to get in the game, where do you invest your time and energy? You take every clue you've got. Then, you run it down in another experiment. You go, "God, that was just wacky, stupid idea."

You get 1 out of 10, I'll take those odds when we're dealing with the problems that we're dealing with. I think that people, hopefully, want to help us solve the problem. I hate it when you do something public, like there's some people saying, "Yeah, but you didn't talk about this. You didn't talk about that." In my experience, it says, "The goal is on the average to get to the individual." If we don't get any signal on average, we don't have a fighting chance of what's in the individual.

We've just got to be willing to be patient and iterate. Take the clues when they come. Do rigorous experiments, not overstep our data, and work toward, if we've got an important lead, how do we make it cost-effective, and how do we fight for it. We can't fight until it's ready. In a disorder where people take their own lives, pressure is on. We only go as fast as we can because if we do it wrong, we won't get to do it at all. That goes for the brain stimulation experiment. It goes with the imaging experiments. All the same, people have short attention spans.

You're smart, even a little bit once, and it doesn't replicate quite like everybody's move into the next thing. Know you got to learn from what didn't quite go right that I thought before. I thought area 25 would always turn down. I only did a study of how cognitive therapy affects your brain to prove that the final common pathway was area 25. We did the cognitive therapy experiment. It was going in the wrong direction. Area 25 wasn't event there. The frontal lobe wasn't going up. It was going down. I kept telling my poor student, my image analysts, "You're obviously putting in the data backwards. Do it again."

After the third time, and sitting down, and doing it myself, it was like, "No. I had a preconceived notion of what it was going to be. I wasn't right. Let's now look at it. Let's think about, how are we so wrong in our hypothesis? Actually, reframed it without the coming to the prior of our own bias, and made, for us, a leap in how to think about it. That's' what led to setting up the next experiment. We are not on the wrong planet with this. We may be on the far side of the moon still. We got to go on this side of the moon, but we're in the right approximate space.

When other people start to get to where that, "Yeah, it's obvious" stage rather than "Yeah, a neurologist stayed over there and just leave us alone," and everybody wants to be in the same space. That's when we can make the big progress. Now, it's like, "Bring it on. You want our data to try and look at it another way?" Well, we're working on having an infrastructure that makes that possible. I have given data to Conor Liston, and Weill Cornell published a very impactful paper in Nature Medicine earlier this year around the time of our paper in Emory.

He wasn't looking with that prospective treatment trial to develop. He said, "Let's throw it into a machine learning algorithm, and let's see if we have different types of brains." He had four signatures. One of them seems to be a signature that can predict response to TMS. That tells me that approach is important. I'm up here. There's a graduate student. He'll take our Emory data. He can go apply with Dr. Liston's methodology. Everybody wants to be in this space now. Now, we can share because we've got some clues of how to do it.

Bill Glovin: Right. Finally, the last question, from your position on the board of the International Neuroethics Society, a few months, *Cerebrum* published an article title “The Illusion of the Perfect Brain Enhancer” about noninvasive brain stimulation. We did talk a little bit about a varying stimulations and planting electrodes in the brain. The article emphasized various ethical considerations of brain stim, something that you also been involved in. There are also ethical concerns about imaging for depression.

Helen Mayberg: I think the ethics of imaging and typing is that because (A), we don't know that a brain type at the beginning is the brain type you'll have with every subsequent episode. Being locked in ethically, it'd be "Well, this is your type, so that this is what you will be entitled to in terms of allocation." We need to be careful that that doesn't constrain the allocation of resources. It would be one ethical concern. Any more than if you have a pneumonia type one, it may not be the same thing type two. Even in cancer, you have a recurrence. These markers may morph new traits. I think that's not an ethical concern. I think that's part of the biology.

I think one of the ethical things is the notion that there are ways to get scans now. There are shots. I'll call them that, imaging centers that are fee-for-service. Come in and get a scan. We'll tell you how to treat. They make lots of money. They make claims that are not based on science. They're very busy. They're very expensive. They don't take insurance. There's already and has been for a long period of time of people who we spent all this time talking about the need for rigor, the need for the experiments, the need for these teams, the need for statistics.

Just because you have 50,000 scans, and you think you know that there are patterns, what is the evidence that demonstrates that your predictions are true? There is the ethics of these scans are available. They are safe. I mean, this is not like someone is mixing up a batch of something in their basement and selling it on the street. There are commercial agents that you can buy. They are approved for scanning the brain, not otherwise specified. Insurance may not pay, but people have credit cards, and claims are made. I think that is an ethical issue that's present now.

Who takes that on? It's been taken on. I've written about it in ethical circles. I've written about it in radiological circles, as have others, that if we're going to have tests, then they need to showed that the tests do what they claim, whatever their costs, and that they're safe, and that you can't have the cart before the horse, so that if things are done without the rigor of the evidence-based proof, that actually is bad for scanning, and it's bad for the treatment of the things that are being scanned, besides the exploitation of what may be desperate people who are ill, who have not responded, and are looking for a way to feel better. We'll do what it takes.

If you spend a lot of money that could have been used for a different kind of second opinion, or someone who might engage in a trial and error with you, the public needs to be aware that these are not ready for primetime. It's our job to do the experiments to prove it or to do the experiments, to find a surrogate that would be more easily implemented, and that the same logic will be true for understanding who gets ketamine or not, who gets ECT or not.

There are experiments now with James Morrow at Sinai, where they're looking to look at people who come in who are very resistant. What's the difference between the outcomes between getting therapy or ECT when that's going to be the treatment of choice. I want an imaging on the front side of that to apply the exact same logic we did for Gerber Therapy. The logic of what we want in every stage of illness is to be able to match people to the treatment that's best for them.

I think the issue in the ethics of all of this, just as an aside with the noninvasive, what's very, very clear in our work and to separate the noninvasive treatments from the invasive. Invasive treatments now are experimental to get people functional. It's to correct a broken brain, an intractable treatment resistant or treatment resistant state. It is, "Well, who would have brain surgery?" People have brain surgery for all kinds of things. The issue is if nothing else available works, the benefit risk ratio can be assessed. I'm not asking you to remove a body part, not cutting something out.

We're tuning the brain with these devices, but they are implanted. I'm celebrating 11 years of one of the patients, the first patient in Atlanta. We have patients from 2003. People have a pacemaker, and many of them continue to have fully functional lives. They need the pacemaker. That's that. Noninvasive, we still need to know that if you can get out of an episode, do you continue to have another episode? We know with the invasive device, if it breaks or the battery dies, you don't have a full-blown episode like you started with, but we don't fix this. We don't cure it.

The same thing if you are taking a pill, and you take a course, or you get a course of TMS. What's its longevity? Ketamine can be miraculously effective in a day. The problem is it doesn't last. Okay, I'm feeling better now. I don't want to kill myself. The question is, how long will it last? If it last long enough to respond when I add something else, fantastic. If you still don't respond to the other things that led you to ketamine, then we've got to come as they're doing. Dr. Charney, Dr. Murrow, people at NIH had a huge work. There's pharma companies who are working on Ketamine derivatives. What is the dosing cycle? What is the safety profile? We're still back to who should get it. There's something about this illness that stress may set people off. People remain unstable. You may need to have something in your system all the time, a question we don't understand.

I think the ethics, and even thinking about, "Well, why would you have an implant? If you're in the same circuit, just do it from the outside." Well, the problem is by studying the circuit, yeah, that logic is true, except if the wire is broken from A to B, then I need to go to B directly. If the wiring and the connections is intact, then maybe I could from the outside in. I think, again, back to the biological logic, got to know the whole system. You can't focus on any one region any more than I can focus on area 25 alone. I mean, as a little point on that.

Everybody who gets DBS (deep brain stimulation) when you put it in the approximate spot down regulates area 25. That does not determine if you get better or not. It's only if you get into the rest of the network. That observation led to searching with a new set of tools, which my colleague, Ki Sueng Choi, who's going to be coming up here, was the lead on.

Being able to map the white matter connections with a special kind of MRI scan, we could look at how could a millimeter and a half difference between one contact on the DBS lead differ stimulating there from the adjacent contact all on the same electrode. If you move it, someone got better. If you left in the same place, they didn't. It's all about the connections, and so that we can revise how we even do the targeting by looking at the connections and making sure we're getting into the full four set of connections.

I couldn't have predicted that initially, that it could have made that insurgent styles out of that. We were out of our minds. I said, "Let the data tell us that this is the wrong logic." Data told us, while you can't see the difference, then let's test it prospectively. See if it makes a difference." I looked at the noninvasive. If noninvasive can work for you, use it. You shouldn't come to me.

In the same way that if you were to assign order, I would say you just start with therapy, least invasive. The problem is that you could shape the brain. Then, when it didn't work, and you go to drug, you might not go back to get the therapy that might actually be more advantageous when your brain is corrected or changed. Now, it can receive it.

I think that even with the brain stimulation, the brain has to be in working order. It needs to undergo plasticity. Then, it needs rehab. I mean, if you have a broken hip, you run a marathon, you need a test to know that your hip is aligned.

First thing you do if you haven't done anything a while, you got to sit and just learn to stand. Then, you got to build up your quadriceps. Then, you get into heavy training. There are stages, none of which can happen until the hip is replaced, whether it's your car, your hip, your brain. These are plastic organ. All these things, you have to do in the right order, or you give up on something that actually was something you needed, but not right now.

Bill Glovin: I think that's a great place to end. Huge thanks to Helen Mayberg for coming into our Dana offices. I like to also say a thank you to our IT Director Jim Rutt for setting up the technical aspects of this face-to-face podcast. Again, you can find Helen and Boadie Dunlop's article at Dana.org. Join us later this month when I talk to Joe LeDoux at the Center for Neural Science at NYU on our upcoming feature, "Well Being and Subjective Experience." That's all for now. Thanks for listening. Happy New Year to all.