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From the campus of Harvard Medical School, this is Think Research, a podcast devoted to the stories behind clinical research. I'm Oby.

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Growing up, Dr. Martha Shenton was fascinated by people different from her. She wanted to know their experiences, their thoughts, and feelings. As a young woman interested in the mind, she chose to pursue the study of psychology and schizophrenia.

Now Dr. Shenton's career has led her to researching imaging techniques of the brain to closely examine neurons and connections. She sits down to talk about her work and how early mentors influenced her research path. Dr. Martha Shenton is a professor of psychiatry at Brigham and Women's Hospital and the director of the psychiatry neuroimaging lab. Dr. Shenton, thank you for joining us. Welcome to the show.

Thank you for having me. So you have dual appointments in psychiatry and radiology. Your primary appointment is in psychiatry.

That's correct.

And your research looks at schizophrenia and traumatic brain injury. Can you tell us how you started your research career and how you became interested in schizophrenia?

Well, I think I was always interested in kind of abnormal psychology and people who looked different and sounded different. I was brought up in Concord, New Hampshire, across the street from the state hospital. And I used to see the psychiatric patients walking around on the grounds.

And they were talking to themselves. And they were acting different. And my friends would pretend that they didn't see them.

And when I was really young, I used to think, am I seeing something that they aren't seeing? And then I came to realize that they felt that there was something wrong with them. So they tried to sort of push it aside, and I was more curious. And in fact, when we played hide and seek, I always won because there was a patient who sat across the street on a bench who would always point out where people were hiding.

So I thought that was kind of interesting. And then next door to us, the superintendent of the state hospital lived, and the patients would be raking leaves. And I just thought it was interesting that here's a group of people that other people kind of don't act as if they exist. And what's going on? What's different about them?

I mean, don't they have parents? Don't they have families? Why are they locked up? And so I guess I was very curious about them, and it was also a time period where phenothiazines weren't quite available. They were just coming out in the 1950s--

What are phenothiazines?

Those are antipsychotic medications. So when I went to bed at night, my bedroom was on the side of the state hospital and big brown building was back a few buildings from the street. But at night, I could hear patients sometimes scream at night.

And I'd have my window open because it would be summer, let's say, and that's how I went to sleep. And I just thought everybody grew up that way. So I became fascinated really early on about, what is it about these people that makes them different? And do they have the same feelings?

Are their thoughts different? Why are they acting in ways that other people don't even-- little children sort of know certain ways to behave and what's expected of them. And so I became curious about mental illness early.

And so that brought you to studying psychology?

I wasn't a great student in high school. I think I'm an anomaly in that way. I was exceedingly bored in high school, so I graduated in the bottom half of my class. But I wrote the president.

At that point, we lived in Rhode Island. And I wrote the president of the university saying, I know I'm a late bloomer. Please take me because they didn't have to take anyone that was in the bottom half of their class.

And I went to the University of Rhode Island. And I loved it. I mean, it was a whole new experience. But I felt like I was outgrowing it fairly quickly, and so I decided to transfer in my sophomore year.

And I chose Sarah Lawrence for creative writing, BU for anthropology, and Wellesley College for psychology because those were my interests, and I got into all three. And I decided to stay in the Boston area. I had a boyfriend who was playing in a rock group at the time.

And so I went to Wellesley and majored in psychology, and I wrote my first term paper on schizophrenia in my junior year. And again, going back to this interest in mental illness and what causes it and learning more about the symptoms and also realizing that it wasn't like other illnesses where you could say, OK, let's check. Does that person have a fever, or what are the other symptoms that would give you a clear diagnosis or a blood test?

These were disorders where people used a menu to basically classify symptoms. And that's not so much the case in other disorders, and it makes it very hard to really know that you have a homogeneous group. But even in cancer, I mean, you can have prostate cancer, but it could be caused by a genetic influence or other things. But still, it seems a little more straightforward than neuropsychiatric disorders.

So talking about the difficulty in diagnosing mental disorders or the difference between mental disorders and other disorders, like you said, like cancer, where you have a tumor or something that you can see, with your appointment in radiology, you're looking at images. You're imaging the brain to try to figure out what the structure of the brain is telling you. How are you doing that on your research?

That's an interesting question, and it brings us away from symptoms to trying to look at brain structure. And people have long suspected that there might be differences in the brain, and that goes back a century or more. But they weren't really good tools for looking at the brain. And so there's a famous person by the name of Plum who said that schizophrenia is a graveyard of pathologists because if you've spent your lifetime trying to figure out schizophrenia by looking at their post-mortem brains, you were wasting your time. And I think there's a lot of truth to that.

But science also evolves by the new methods that you have in order to look more closely. And CT scans came in the 1970s, and that allowed you to look at brain versus fluid. You couldn't differentiate gray matter or white matter or the different structures in the brain.

And then in the 1980s, magnetic resonance imaging came in, and so that allowed you to really look at gray matter and white matter and even start to begin to look at tracing the ventricles, which is a fluid area in the brain that get larger, say, in Alzheimer's disease. And people would take tools to measure by hand the intracranial cavity versus the ventricles in the brain to see the brain versus the fluid. And that was still very primitive, but it took computer scientists really about 15 years to be able to take the Voxel information that you have on the images and really start to differentiate brain tissue into gray matter, white matter, and cerebrospinal fluid.

And so that was a huge, huge increase. And also, you were going from one centimeter slices where you do 12 of them through the brain to 1.5-millimeter slices through the entire brain. So the resolution became better.

There were more tools to use and we're able in the early '90s. We were able to basically state, yes, schizophrenia is a brain disorder. And some of the abnormalities included smaller superior temporal gyrus, which is in the area of the temporal lobe where things like auditory processing take place and might be related to things like auditory hallucinations.

And we found that they were related to formal thought disorder. And so this was a step forward in an understanding that this is a brain disorder, not like in the 1950s where mothers were blamed for their child being schizophrenic. No, well, they weren't told they were schizogenic mothers, but that was the term that was used.

So tell me more about that. They thought that something that the mother did caused or there was a genetic--

No, this is a time period where since there were no causes known, therefore, it was OK environmentally induced. It was the mother. It was the way the mother treated-- it was cold and didn't relate well to the child. You can imagine if you were a mother, and you're doing everything. When, in fact, it had nothing to do with the way the mother was treating these children.

Now there are genetic predispositions for developing schizophrenia. It does run in families. It's also genetic.

And there were seminal studies that my mentor was involved in Denmark looking at twins that were adopted away from home that were monozygotic versus dizygotic twins or identical versus not identical, which makes them similar to being siblings. And the rates of schizophrenia were higher in the identical twins who were adopted away compared to the nonidentical twins, suggesting that this is something that's biologically driven. And so over the course of the 20th century with improvements in imaging, scientists, doctors were able to see that the brains of schizophrenic people looked different than people that were not schizophrenic.

Pretty much-- I mean there's some inconsistent findings, but in general, I think the structural data is pretty clear that there are certain areas of the brain that tend to be reduced in size compared to normal controls. And functional MRI also came in where people looked at how the brain activity responds to stimuli. But early on, once we're able to look at the brain, people would look at say the hippocampus, particularly amygdala hippocampus and PTSD post-traumatic stress disorder, because we found was actually smaller. And we also found in a study of Vietnam twins that those who ended up being exposed to combat and had smaller hippocampus, they're monozygotic. Their identical twin who wasn't exposed to combat also had a smaller hippocampus compared to others, suggesting that there may be a predisposition to some of this.

Now it needs to be carried further. What does that mean? Where do we go from there? But I think that being able to view the brain while people are alive is a huge step forward.

And this really only became something that people could do in the 1970s with CT 1980s, early '80s into-- I think our paper in the *New England Journal* was in 1992 that got a lot of attention because it was one of the first studies where you could actually not only just measure something like the amygdala hippocampal complex-- hippocampus being involved in memory and amygdala being involved in emotion-- but you could create 3D structures of it and visualize it. And this is all because of the assistance and help of computer scientists in taking on the role of trying to really quantify and measure and visualize. And this has also been really important for doing neurosurgery.

So later in my career, when I did work at in radiology at the Brigham, I had a mentor Frank Jolesz, who was a real visionary. He really wanted to develop non-invasive neurosurgery.

What is computer science allowing researchers and clinicians to do now that's improving imaging of the brain?

Basically, it's the post-processing that's important. So the images are there, and radiologists or neuroradiologists are trained to say look at the brain. But they're trained to pick out things like a tumor or something that's visually abnormal, and that's what's important for a patient who's coming in, say, with a traumatic brain injury.

Does that person need neurosurgery? Is there blood in the brain? Those things can be seen very quickly.

But if you're looking at a disorder like schizophrenia or you looking at a disorder like mild traumatic brain injury, also known as concussion, those things don't show up most MRIs and most CTs don't tell you anything when you look at a schizophrenic brain. They might say something like, if it's a patient with schizophrenia, enlarged lateral ventricles within normal limits because their template is pretty large. They note that there's something large, but it's not clinically significant, particularly. So they're looking for very big differences.

And what computer scientists can help us do is to extract information from the images that allow us to measure at a Voxel level. And also, the first thing that we got help from computer scientists with was to be able to classify, looking at the signal for white matter and gray matter and CSF on those images to say this is the range for white matter. This is the range for gray matter.

This is the range for CSF, and that sounds like a fairly simple thing to separate something into three classes of tissue. But it took them 15 years to do that. So that was a big change.

And people started looking at individual areas of the brain and sometimes relationships between areas of the brain, for example, the superior temporal gyrus that I talked about before and related or correlated in these patients with schizophrenia with the amygdala and hippocampal complex. And it was more on the left than on the right. But what people are doing now is they're looking at brain connections. The whole notion of connectivity is huge.

And so if you look at the National Institute of Health, you can see the human connectome projects. What are those about? And the first generation of those studies were to take the best data that we can get today and to collect data in the same way with the same toolbox of behavioral measures, along with the imaging measures, and to tell us something about the human brain using diffusion imaging, which is a way of looking at water in the brain, which I can talk about a little bit more, using functional imaging, structural imaging. And then the children of those of the first parent human connectome MPI, for example, it's the human connectome for early psychosis. So what we're doing is trying to use the same methods and collect data on 400 subjects-- 320 patients with early psychosis and 80 with who are normal controls.

And the reason that it's 80 and not larger is because we're going to be able to use data that's collected from the parent grants looking at controls. But what we want is that small number of 80 in order to make sure that there are no within variance differences in the magnets that we're using, which is another big issue today as people start to realize that big data is important. And you want to collect as much information you can. But you want to make sure that the data is harmonized or homogeneous, and that you're not having a magnet in one city that's measuring something very different than in another city.

What's interesting for doing research for large samples is if you can do this automated, you're not confined to small samples. But at the end of the day, you want to be able to take what you learned from the large data and go back to the individual person.

When I started out in 1988 is when I got a Career Development Award from NIMH. I really wanted to learn about the brain, so I wanted to get training. And that's why I came to the Brigham to work with Frank Jolesz. And he hooked me up with Ron Kikinis who came in as a postdoc, as I was. And so what Ron set up was a presurgical planning for neurosurgery.

What he wanted to do is to develop tools that could be used by neurosurgeons. And so my small group used the tools that they were developing, and I think there was maybe a couple of computer scientists at that point. And our job was to point out, well, you've got the largest white matter area in the brain backwards. It doesn't matter when you look at it. If you think about it, a computer scientist looks at a bottle like this.

It doesn't matter. They can measure it. What difference does a position make? But if you're doing neurosurgery really does make a difference?

And so some of the things that have been developed, which are really good for presurgical planning is we have someone in our lab right now who's developed a method, and we haven't talked too much about diffusion imaging, at this point, but it is a way of looking at water in the brain.

And why is that important? Why is diffusion imaging and looking at the water in the brain important?

Well, if you have a tumor in the brain, You have a lot of edema. And if you're going in to do neurosurgery, that edema might be covering up some areas of the brain that you don't want to cut into that aren't tumor, but you can't really see it on the scan. Now if you could see it ahead of time, you could plan your surgery a little bit better. And so, for example, Ofer Pasternak in our group has developed a method called free-water.

So diffusion imaging is based on looking at the directionality of water in the brain, and the principles of very simple. The physics and the math is very complicated in some ways. But basically, if you drop water into a bowl of water, it disperses in all directions. But if you were to drop ink onto a newspaper, it's not going to go in all directions.

So it's not going to be a sphere. It's going to be restricted by the fiber in the newspaper. And that's the same idea as looking at the brain.

If you're in CSF, it disperses in all directions, and it's a sphere. If it's in white matter, it's restricted in directions, and so it's going to be bi-directional like a tube. And the more restricted, the more likely you are in white matter.

And what Ofer developed as a way of refining things even a little further. He can look at water that's closer to tissue and water that's free-water. And if you can remove the free-water, then you can get rid of the edema--

So then you just see the water that's next to the tissue?

Instead of the water, you're looking at a tumor, and there's some water. It looks like some swelling that's in the tissue, but there's a lot of swelling outside. And then you remove that. The surgeon can actually see, and the virtue of what's been done for visualization is you can move things around.

And you can move parts of tissue out, so you can get a better look from a different angle. All of this is presurgical. So you can look and see, oh, there's corpus callosum in there.

I don't that's the main connection between the right and left hemisphere. I don't want to touch that area. I'd like to stay away from that. I couldn't see that before because even with diffusion imaging, which should show white matter, there was so much edema in there. I couldn't see it.

Now you remove it, and you can see that the white matter is somewhat damaged. But you don't want to pull out the white matter that isn't tumor, and you also classify the tumor. It has a different signal intensity, so it has a different label or a different color. And you can pull that out. So that was all work that was done in the 1980s.

Well, not the free-water-- the free-water was done later. But the whole notion of segmenting the brain and algorithms was done early, and now it's gotten much more sophisticated. And so it helps with neurosurgery cases.

We're also hoping that it eventually will be able to develop some biomarkers. Like I know Alex Lynn, who works with me on some of the NFL studies that we're doing, he talks about having a biopsy of the brain-- a noninvasive biopsy of the brain. And I think we have to think more about coming up with reliable measures that go beyond, particularly for psychiatric disorders where you're relying on symptoms that are not so reliable. The diagnoses a lot of symptoms go across different disorders.

So it would be nice to come up with measures that are more reliable, that tell you something about a change in the brain, and then you cluster your patients based on some of these measures and see if it makes a difference. Because right now, you could have a clinical trial and assume that all your patients say with schizophrenia are the same. And your clinical trial fails because they aren't the same, but there's a small group of patients that maybe have attentional network problems that would respond to this new drug. But if you have everybody else in there, you're going to lose your ability to show that, hey, there is a subset of patients who really respond.

Let's go back a little bit to some of the discussion we had about Frank Jolesz your mentor. Also, Philip Holtzman was one of your mentors.

Right and Bob McCarley. Those are sort of the three main mentors I've had.

Could you talk about how they're teaching and working with him has influence to you in your career?

This goes back to graduate school with Philip Holtzman, who I mentioned was a seminal researcher in the field of schizophrenia, and he came and gave graduate students in a proseminar a talk. And one of the things he was talking about was eye tracking that patients with schizophrenia track differently, and there's that kind of jerking in their eyes. They don't track it exactly, and they developed in these digital ways of looking at it. And that this was somehow more related to the disease itself than something like auditory hallucinations or delusions, which are really-- I mean, that's the first thing that hits you.

If you sit down and talk with a very psychotic patient is they really talk differently. They're telling you things that are not the case that, no, that person out there is not out to get you. Those stand out so hugely that I thought they've got to be related more to the disease than something like eye tracking, and the idea that something that you think has nothing to do with the disease could end up being related to the disease kind of fascinated me.

And he also talked about the genetics of the disease in his studies in Denmark and the twins. And he was also someone who was really very excited and passionate about science. And so that was contagious really, and it was fun to listen to him and to talk with him. And I guess I became sort of even more interested in trying to understand schizophrenia, using scientific methods than just observing which had been my previous experience.

And so he was also very caring, and he was very supportive of his trainees. And I felt really fortunate because that's not always the case. I think it's really unfortunate when someone is with a mentor that doesn't have them on their radar, that isn't really helpful because so much of the first part of any scientist's career is the apprenticeship. It's hugely important. And the person that is your mentor has to really take an interest in the trainee.

Otherwise, it's not going to work. It doesn't matter how bright the trainee is. If you don't have a good mentor. It can really interfere with your career.

So I felt really fortunate there. Then Bob McCarthy was really brilliant. I worked with him as a postdoc after Phil Holtzman, and that was my introduction to more physiological measures looking at event-related potentials, which is really looking at an EEG but you're introducing the stimulation.

So what was interesting there is patients with schizophrenia have trouble figuring out what's relevant and irrelevant. And what was really interesting is they had the same responses as someone who is not schizophrenic, but it was reduced in magnitude. And why is that? And that was kind of I was curious about that.

And you could look at something in very short time, which I thought was fascinating, but I wanted to get closer to the brain than measuring from the outside of the brain. And that was my introduction to Frank Jolesz.

And my first meetings with Frank Jolesz. I didn't know him at all. So I was walking in cold, asking, will you be my mentor on a career award? I mean, why would he say yes?

But I thought I have nothing to lose. And that's the thing I would tell young people. When you have nothing to lose, kind of go for it. I mean, what's the worst that can happen? Someone says no.

And so I talked to him. And he said, oh, come back, and he was very interested more to know about me, how I thought. And this was all very nice, and I came back to meet with him.

And I met the same person I had run into when I'd walked in before. And he said, oh, you're one of one of people. And I thought, oh, that's kind of nice. I would like to be thought of as one of Frank's people.

And Frank basically told me that I was wasting my time, and my jaw kind of dropped. And I said, well, will you still be my mentor? And he said, oh, of course. But I just want you to know you're wasting your time because if anything were to be found with imaging, it would have already been found in schizophrenia.

And so he was willing though to mentor me despite that. And I actually thought a lot about mentor and mentee relationships. And I'm a PI on a T32 training grant. And I used to think that it didn't matter whether you liked the person or not. If they were brilliant then that would be sufficient.

And over time, I really figured out that this apprenticeship relationship is so important that you want to pick someone that's not just brilliant, but also has the time for you. You want to look and see that junior people are first author on a lot of papers, that the person is generative, that if you hand in a paper, you're not going to wait five months before getting feedback. You really want to know that you're on that person's radar. And that's critically important picking out a mentor.

And also the idea that you don't just have one mentor-- you can have a scientific mentor. Or you can have someone that knows the politics of academia as a mentor. You want to have different mentors in your life, and senior people are actually pretty-- my experience when I was a trainee was they were pretty open to if you wanted to go to them to get help for putting in a career development award or something.

They were usually pretty open and helpful, and even talking to trainees and labs is a good way to go. But that critical period early on in one's career is so important that without that mentorship, you could get left behind and not end up doing what you really are hoping to have a career in.

And the thing that a young person has to remember is their ideas are valid. They want to have a conversation. They don't want to say, OK, I want to do something that pleases my mentor.

That's never going to be satisfactory in the end. And it's so hard to get grant funding today and so hard to be a scientist that you have to have a passion that you want to follow. You may be incorrect, and at a certain point, you say OK, this isn't working.

Is there some other method I could use? Or how much are you married to it? Or this is not going to get funded right now by NIMH, let's say. You put it on a back burner and say, OK, I'm going to focus on this other thing that I'm not as passionate about, but it's doable.

And when I get funded, I'll do that work, but I'll also see if I can't find other methods that will help me with this other area that I'm really pretty passionate about that isn't likely to get funding. And you want young people to feel that they don't have to just please their mentor. If they're only trying to please their mentor, how are they going to sustain a career?

So I would advise people to look for a mentor where they can have a dialogue and have a mentor. It's a two-way street. I mean, training has to be able to say back.

Well, I'm not sure I agree with that. I don't, or I don't follow it. Like, why do you think x? It should be a dialogue, and there shouldn't be concerns about that kind of interplay.

And I've had a trainee where I've had to say, but you gave up your idea too soon. That's not what I meant. Tell me why, convince me.

Do you have any other experience that you can relate in terms of like picking a field or deciding where to go for training or any other advice?

I think some of the most exciting areas have been where there are no guideposts. You're doing something that's pioneering, and other people haven't done it. And I don't think one should be afraid of doing that.

But I think one has to, if you want to be an academic researcher, you also have to, like in baseball, look at the ball. What do you need to do? You need first author publications. You need grant funding, but you also need to look at the whole picture.

Like what are you passion about? What is it that you want to do? What are your questions?

What do you want to discover? And you might not have all the answers. But what I think I would tell people is find a lab that you can go to that the work excites you that's being done there.

Find a mentor who however busy they are and they're an expert in the field and they travel, they have a reputation of being generative. They have a number of junior people. And you have to be curious, and you have to follow your nose, really.

Dr. Shenton, thank you very much. This is a great conversation. Thank you for coming in.

Next time on Think Research, and so he turned to me. And he said, if you want to help patients, you're really going to need to simplify your approach. And so I started thinking from that moment onward how can we really simplify what we're doing at every possible stage.

Dr. Jeff Karp discusses his innovative approach to critical thinking and problem solving. Thank you for listening. If you've enjoyed this podcast, please read us on iTunes and help us spread the word about the amazing research taking place across the Harvard community.

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