

**Dr. Karen Berman**

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### **Dr. Karen Berman Interview**

Claudia Wassmann:

So this is Claudia Wassmann and today's date is Wednesday, February 23<sup>rd</sup> 2005 and I'm conducting an interview with Dr. Karen Berman. Okay Dr. Berman you are the Chief of the Unit on Integrative Neural Imaging and the --

Dr. Karen Berman: It's actually the Section on Neural Imaging now.

CW: Yes, so what is the above unit? The unit is called how?

KB: It's the Section of Integrative Neural Imaging.

CW: Okay. Could just start with telling me when did you come to NIH?

KB: I came to the NIH in 1980 as a young fellow right out of my residency training.

CW: Where did you do your residency?

KB: At the University of California at San Diego in the Department of Psychiatry.

CW: So you were interested in psychiatry?

KB: Right.

CW: And what brought you to NIH?

KB: Well I think that as I was involved in my residency I got particularly interested in the severe mental illnesses, particularly schizophrenia. I felt that seeing this dissolution of everything that makes us who and what we are in patients really told me a lot about what makes us human. At the same time I felt very frustrated that there was so little that we could do to help our patients with severe mental illnesses like schizophrenia. We could sort of ameliorate their systems a little bit with neuroleptic

medication, but there was no cure particularly for the cognitive problems that these folks developed. And I think that's what drove me to want to do research in the field and to come here to the NIH.

CW: At the moment when you came here how did you study these patients?

KB: There was actually very little that was available to us and I remember for the first couple of years that I was here participating in drawing blood and collecting urine, doing CSF samples from spinal taps, very peripheral ways of measuring what was going on in the brain.

KB: So thinking about what was really an emerging field right then, brain imaging, was very exciting to me because it was a way of directly looking in the brains of our patients. Another thing that was very exciting to me was a paper that I had seen I think in about 1978 or '79 when I was resident and that paper was by somebody who I later came to work with here, Dan Weinberger, and he's been my long term colleague throughout all my years here in brain imaging, but his paper was very seminal because it showed using all we had at that time, CAT scans that the ventricles in patients with schizophrenia, that is to say the fluid filled spaces in their brains were actually larger and this showed I think for very close to the first time that there really were brain changes that accompanied this illness and it was very important to moving the illness out of the spectrum of stigma, thinking that these folks have poor will or bad mothering — interesting that they never talk about bad fathering, it's always bad mothering. But you know those were sort some of the things that people thought about in terms of understanding schizophrenia at that time and studies, being able to look in the brains of folks really was a way to show that this is a disease like any other, like diabetes, like heart disease and it also gave us hope that we might be able to fix it with medical interventions. So that's sort of where I was at when I came here. There were very few methods to look at the brain, CAT scans as I mentioned to look at brain structure in a very primitive sense because CAT scan doesn't look at soft tissues very well. In addition what we really needed — in addition to a way of looking at the soft tissues of the brain structurally was a way to look at how the brain functions. When I got here, as I said, I spent a couple of years just doing peripheral measurements of things in the blood or the urine or the CSF. I did a few studies with rats until I found out that that was not something that particularly enjoyed doing, but this field of brain imaging that was just emerging seemed like so

much better of an approach to this. And my colleague Dan Weinberger and I acquired a Xenon-133 inhalation machine for measuring regional cerebral blood flow, and this was by today's terms a very primitive way of measuring blood flow in the brain as a proxy for neural activity, but it allowed us to look at function. It only allowed to look at function in the top centimeter or the cortex of the brain, not deeper structures and its resolution, its spatial resolution. In other words its ability to tell whether things are far a part in the brain or not was quite limited to about two or three centimeters which is pretty big in terms of brain structure, but none-the-less this was a very exciting brand new pioneering way to look at the brain. And Dan Weinberger and I put together what was really the first free standing nuclear medicine facility in a psychiatry hospital. At the time we were over at the NIMH's facility at Saint Elizabeth's Hospital, which was a wonderful place to be conducting research on psychiatric patients, particularly schizophrenia and that facility was an asylum in the true good sense of the word. They really had a community of folks with mental illness. They had an upholstery shop and their own creamery and places where the patients worked. It was true community and an asylum in a good sense. At any rate at that time it was a very good place to be to study severe mental illnesses and we set up our shop or Xenon-133 inhalation machine for measuring regional cerebral blood flow there. We were able to measure blood flow in the brains of our patients while they were performing thinking tasks and this was another thing that was very pioneering at the time because it allowed us to see what goes wrong in the brain during the kinds of thinking that we know our patients with schizophrenia have troubles with.

CW: So the reason why you were so interested in function came from the observation of your patients?

KB: Exactly. That's exactly right and that's always been the guide. In schizophrenia research and really in all mental illness research you really have to use sort of a top down approach where you start with observations from patients. We have no lab test at the currently that are diagnostic. So you start with observing your patients and that allows you to make inferences about what's wrong in their brains and then you study those brain systems and that's really been the guiding principal all along.

CW: And how have these brain-imaging techniques changed your understanding of the illness?

KB: Well as I say this first study that I saw from my colleague Dan Weinberger in '78 or '79 that showed a real structural change in the brains completely moved the field away from thinking that this was something social or you know just poor will power or whatever to making us thinking about the biology of the illness and it allowed us to think about new ways to intervene in the illness. As we've refined our knowledge with brain imaging and now with genetics and we're starting to put genetics together with brain imaging which is really very exciting we really are beginning to home in on the real problems, the etiology of schizophrenia and I think that we'll be able to develop more incisive treatments rather than using techniques that are sort of like sledge hammers that instead of speaking to particular parts of the brain and particular ways that the brain dysfunctions just sort of treating the whole brain.

CW: Yes. You mentioned it already you're going to imaging genomics as you call it. Can you tell a little bit more about that?

KB: Okay. In schizophrenia, as mentioned, we start with observations of patients. We know have a lot of information about genes, but the observations from patients and what we know about them and right now we know two things very, very well. One is the frontal cortex in schizophrenia is abnormal and a lot of that came from our early work using this old, old method of Xenon-133 inhalation regional cerebral blood flow. The other thing that we know is that the dopamine system is abnormal in schizophrenia. So this would mean that we want to find-we want to look at genes that have to do with frontal lobe function and dopamine. Dan Weinberger and his group have found that COMT, catechol-o-methyl transferase, is a gene that increases. If you have a particular variation in that gene it increases your risk for schizophrenia. A lot of wonderful brain imaging work is coming out now showing that gene does affect frontal lobe function, and how exactly it affects frontal lobe function.

That's an example of the top approach where you start with the patient you look for what's going on in the brain and then you try to find genes that really underlie these problems. Another important way, and this is something that my group is doing right now very actively, is sort of a bottom up approach and we're studying an illness called William's Syndrome, which is a very fascinating illness. It's a genetic illness. We know the genes. We know that about 21 genes on chromosome 7 are hemi-deleted in this syndrome. It's a spontaneous mutation. It's really quite rare, but patients with this hemi-deletion on chromosome 7 are just

fascinating because they have a very specific cognitive disability and that is disability in the visual spatial constructive domain. In other words they cannot see an object as a set of component parts and they cannot rebuild an object if given those component parts. They can't visualize it this way. They can't do very well in jigsaw puzzles, for example. Because we know the genes in this illness and because the cognitive deficits are pretty well circumscribed it's kind of a direct gene behavior paradigm that we can explore and maybe the best one in humans that we've discovered so far. So we know the genes. We know some of the abnormal behavior and cognition. The question that my group has asked is what in the brain is going on? How are those genetic problems transduced in the brain to produce the cognitive and behavioral problems in this syndrome?

So using the top down approach in schizophrenia and the bottom approach to understand how genes affect the brain using neural imaging to come to that understanding has been very, very exciting and in William's Syndrome we've been using multiple modalities of imaging and this is something I want to talk about too, because we now have so many unbelievably wonderful tools that allow us to look at the structure, the chemistry and the function of the brain. This is how we've approached both our top down search in schizophrenia and our bottom up search in illnesses like William's Syndrome where we know the genes. So we've applied structural imaging and we've found in William's Syndrome abnormalities in a part of the posterior parietal cortex that helps the brain to understand where in space objects are. With functional imaging we've found that some areas just forward of that structurally affected region in William's Syndrome don't work right and putting all this together we know have an understanding of how the visual spatial constructive disabilities in William's Syndrome work. Because we know the genes that are deleted in this illness we know -- we have some clues about which of the genes in that region might play a role in this. So I think that's a good example of how we can use neural imaging to understand how genes affect the brain to produce these behavioral problems.

CW: Yes, so you mentioned structural -- the techniques you refer to is this MRI and fMRI?

KB: And PET as well.

CW: And PET as well?

KB: Right. So I mentioned when I first started out way, way back, 20 - almost 25 years ago all we had was CAT scan to look at the structure of the brain and it really doesn't look at soft tissues like the gray and white matter of the brain very well. Once MRI came on the scene and gee that was sort of in the '90s we were able to differentiate between different types of soft tissues. So we could delineate what was gray matter, what was white matter really in a very good way for the first time and this has been a very important tool in our field. Very fine structural resolution of brain matter. The other thing that's happened in terms of looking at the structure of the brain is that we know have methods for putting every person's brain in the same three dimensional stereotaxic space and averaging across individuals so that we can look how a group is statistically different from a control group for example, a patient population. So that structure in function as I mentioned when I first, when we first started out with Xenon-133 inhalation -- Xenon-133 is an inert gas -- and just watching it go into the body and arrive at the brain and disappear from the brain. The rate at which that happened told us something about the blood flow in various regions of the brain. And blood flow, just like when you pump up a muscle and you get more blood flow to that muscle, the brain is very similar when you're working hard with a piece of your brain, it requires more blood flow to deliver more oxygen to take away waste matter from those metabolic processes, etcetera. So when we started out with Xenon-133 we had very poor spatial resolution. We could only look at the surface of the brain and again once topographic methods came online with fMRI and then -- with MRI and then PET we were able to look deep in the brain and our spatial resolution was much better. So PET came on the scene also in the '80s. At first there were only methods for looking at the general function of the brain, fluorodeoxyglucose which Lou Sokolov whose been here who you may want to talk with as a pioneer in this field developed a method for measuring sugar incorporation into the brain and that of course is the major substrate for metabolism in the brain and he developed a way to give the body a special type of tagged sugar that got stuck in neurons for awhile and because it was tagged with a radio nuclei something that gave off a positron emitter, we could put people in PET cameras and measure the function of their brains that way and really get much better spatial resolution. So that was a huge development. People also developed radioligands, ways of tagging specific molecules for, for example, the dopamine system or the opiate system. So we began to be able to look at receptors for those molecules in the brain and not only localize them, but measure them and quantitate them and this has all been wonderful

in addressing mental illness and helping us to understand what goes awry in our patients brains.

fMRI which really started in the, about the mid-'90s and it has just exploded is another new method. Its temporal resolution is much better than PET so it allows us to look in the brain and see what's happening on the order of a few seconds. Now in honesty that's kind of an eternity in the life of the brain and the way we think, but it's a lot better than the PET methods that allowed us only oh about 30 seconds to a minute of temporal resolution and it's much better than our old method of looking at Xenon-133, which was about 2 to 3 minutes of resolution in the brain, which is truly an eon in terms of how the brain thinks.

CW: Interesting. As you are talking about technology maybe you can tell us a little bit more about how this Neural Imaging Section here grew at the NIH. You moved here recently I know.

KB: Well I think that at the beginning this was such a rarified technique and it was so new and so difficult that there were sort of separate groups doing their own research in the brain imaging and everybody had different questions, everybody had different approaches. A lot of the methods that we were using were just getting to be worked out. Something that happened -- this is really across the world, not so much at the NIH, but it certainly affected us -- also occurred in the '90s, and I alluded to this a little bit earlier -- and that was the ability to put the data that we got about people's brains in the same stereotaxic space, and analyze it statistically and get coordinates sort of like latitude and longitude of the regions in the brain that we're looking at. People across the world started doing this in the same way and what that meant is that we really could compare results across the world and this really was a wonderful cross fertilization in the field and I think allowed the field to take off. Karl Friston and Richard Frackowiak were pioneers in developing these analytical methods. So not only has the hardware, the ways that we can actually measure brain structure and function developed, but also sort of the software if you will, the ways we analyze the data have been just as important in allowing us to move forward.

Here at the NIH what that meant was that people started to work together more and now, today, there is a very dynamic large neural imaging community from all kinds of fields, so we meet frequently. So I work in schizophrenia, William's Syndrome and other mental illnesses and cognitive illness, but I get to hear what the people in epilepsy are doing, in alcoholism, drug abuse and you

know hearing about all of these different things here at the NIH I think just provides a unique neural imaging community and a lot of cross fertilization of ideas. We really have a critical mass here both of the hardware that we need and the brains that we need to know how to use it best.

CW: Well you have this picture here --

KB: Right.

CW: -- that you wanted to tell me something about.

KB: Well I was unpacking boxes the other day and I came upon this and this is an example of one these old Xenon-133 brain maps that we used to get and by today's standards you can barely recognize this as a brain, but this is a lateral view, a side ways view of the brain. This is the front of the brain, the frontal lobe. This is the back of the brain here and we're seeing with very poor spatial resolutions how controls respond to doing the thinking task and how patients with schizophrenia respond to doing the thinking task.

I must tell you that at the beginning when I was starting this work we just got numbers. We did not have pictures. It was simply numbers and of course all of the data that we work with now is numbers too, but we're very good at turning it into brain maps. Once we figured out how to put these data into pictures and our colleague Richard Coppola, who is here also now running the MEG facility, was very helpful in working out methods to turn this into pictures. Once we could do this it's amazing, people really began to appreciate this research and it sort of underlined the old maxim that a picture is worth a thousand words, in this maybe a million words, but we found that once we could produce pictures like this people really began to understand what we had found much better than from then numbers. Even though we're all scientists, I think the old maxim is true. You know just looking at this, and I know you've seen brain maps and looked at the kinds of data that we're producing now, the quality, the richness of the data sets that we get now there's just now comparison, but I must tell you that at the time when were just starting out this was very exciting and it was very exciting for the whole field. I can remember as a young fellow when I first presented this was one of my first presentations ever at a national meeting and I presented these data. You know people gasped. People were amazed that we could actually show these differences in how the brain was functioning and where it was dysfunctioning more--most, which

was in the frontal lobes here and that was really an eye opener for people, and of course for us.

CW: So did--once you could see your data as a picture did that also change the questions you were asking concerning the illness?

KB: I don't think it changed our questions because of course we were so immersed in the data and we understood our data so well that we really -- I don't think the questions that we asked changed, but our ability to communicate these findings to the rest of the research world in our field increased and I think really stimulated other people's ideas better.

CW: Okay. I have two more questions.

KB: Okay.

CW: One would be when these techniques, technologies were developed -- so it's the hardware and the software -- how did the needs that the researcher had in the clinic, influence, impact the development of the technology we got.

KB: You mean with patients?

CW: Is there a cross fertilizations between --

KB: You know I must tell you that to some degree some of my -- the same frustration that I mentioned that brought me here, our inability to really cure our patients, really help with what hurts them the most which I believe is the cognitive disabilities still exist to some degree. Even though we have so much more knowledge right now we are not quite yet translating that to the clinic. With the one exception that I believe that brain imaging truly brought the way we deal with patients, with mental illness and their families out of the dark ages when we were really stigmatizing these patients and looking everywhere but in the brain for reasons for what was wrong with them. That's made all the difference in the world, knowing that this is a true biomedical illness that we can fix it to some degree with meds and trying to -- try to improve the way that we do that. Now that being said I honestly believe that we are on the verge of something very exciting and that is the ability to put together this genetic information and our observations, our direct observations of what's going on in the brain, the brains of our patients put those things together. I think that this is beginning to produce the kind of data that will lead to very incisive treatments, treatments that get at the real crux of the

problem. If a gene is not producing an enzyme, a protein that people need to make their brains work at an optimal level perhaps we'll be able to understand how to replace that or how to affect that enzyme and we'll be able to use brain imaging to study whether those interventions are really ameliorating these physiological problems that we can look at. So on the one hand I still have some of that original frustration on the other hand at this point in time with the new genetic information, the new imaging tools that we have, I really feel quite a bit of optimism and excitement, but we're not there yet.

CW: Okay. Well, the other thing that I'm interested in is with the data that you get about the functioning of the brain in schizophrenia patients what do you learn about the functioning in normal brains?

KB: That's a terrific question and I think I alluded to this at the beginning of our interview that I really felt that observing and trying to understand what goes wrong in the brains of patients was a back door.

CW: Oh yeah.

KB: I was mentioning that I've always felt that this was an important way of understanding what makes us who and what we are and I still believe that to a great extent. I also think that the tools that we have are really wonderful in allowing us to understand how we think in everyday life and how we're creative and understanding those systems is a first step to looking at diseases and problems, but seeing how those systems actually go awry in our patients brains I think helps us to understand what is necessary. What is both necessary and sufficient to allow us to function optimally as human beings and make us the unique people that we are. One of the things that brain imaging is teaching us is how individual people are. There's tremendous variability in the -- there's both tremendous variability and commonalities in the ways that we use our brains to think.

CW: Are you finding gender differences?

KB: People have -- that's not something that I have specifically studied. Although I study the effects of hormones on the brain and that's an interest of mine too, but there are gender differences that have been described in the brains of men and women. I think that there's more work to be done in that area personally.

CW: But that is not something that you are looking at when you are...

KB: Not specifically.

CW: No, no. Okay. Okay well thank you very much.

KB: You're very welcome.