#265: Brain traces: Neurobiology's emerging insights into schizophrenia and its treatment

VOICEOVER Welcome to Up Close, the research talk show from the University of Melbourne, Australia.

SHANE HUNTINGTON I'm Dr Shane Huntington. Thanks for joining us. Our moment to moment picture of our surroundings is something we generally take for granted. Our visual and aural perceptions are mostly seamless. But what if somebody told you that some of the things, some of the people even you see and hear were fictional or if your perceived reality was not the same as everybody else's? There's a range of neurological discords that can challenge the certainty of our perceptions. Schizophrenia is one of those conditions. It weakens our ability to distinguish between what is real and what is delusion or hallucination. As with many conditions that affect the brain, schizophrenia is complex and requires innovative approaches to research. But how can we investigate a disorder with symptoms such as delusions or fictional perceptions and what are the most effective treatments for schizophrenia? Today on Up Close we are speaking to one of the leaders in schizophrenia research, molecular biologist Professor Brian Dean. Brian is a senior research fellow at the Mental Health Research Institute, part of the Florey Institute of Neuroscience and Mental Health and Professor of Psychiatry here at the University of Melbourne. Welcome to Up Close Brian.

BRIAN DEAN Thank you.

SHANE HUNTINGTON Briefly before we start talking about research in the area of schizophrenia, can you give us an idea of what the condition is?

BRIAN DEAN As you mentioned, schizophrenia is currently defined by if you like a raft of symptoms. One we're most commonly used to is psychoses and they're the
hallucinations, the delusions, hearing voices, seeing things. But the other side of schizophrenia is actually much more challenging, what's called the negative symptoms. This you see where people, as they have the disease for longer, go into a social withdrawal, stop looking after themselves. And now we recognise the real challenge is the cognitive deficit of schizophrenia. Just to put that in context. If someone with schizophrenia has a severe cognitive deficit and let's say they like drinking tea with milk in. Now, if your milk runs out, you'd know to go down to the shop and buy another bottle of milk. The schizophrenic who has severe cognitive deficits couldn't put that series of actions together and would more than likely just stop drinking tea. Cognition is essentially a word that describes a higher function of our brain that allows us to cope with day to day living. In people with schizophrenia, because of the cognitive deficits, they can have real problems in understanding that for example, if I employ you and you have schizophrenia and I say you have to be at work at 9:00 am in the morning, they have real problems realising that that's something they must do. They'll often just rock up at 1:00 pm in the afternoon and think that's fine. So it's very hard for them to hold down a job quite often. It's also quite difficult for them to then have good interactions with other people because we rely on our cognitive abilities to judge how we're interacting with someone else and often in people with schizophrenia that's impaired. For example, one experience I had was a very nice person with schizophrenia would come and speak very loudly to you, within six inches of your face. Even though I knew he's a very nice person, it was quite threatening. These are the sorts of complex ways that cognitive deficits can affect people with schizophrenia. You can see that really impacts on their lifestyle.

SHANE HUNTINGTON
Brian, when does schizophrenia develop and how does it compare with other mental disorders such as Alzheimer's?

BRIAN DEAN
In males, the peak onset with schizophrenia is usually from about 18 to 23. Interestingly, it's later in females. They peak between about 24 and 30. With Alzheimer's of course that's a disease of old age, onset's usually around about 60. But if you go to the other psychiatric disorders such as bipolar disorder and depression, their peak of onset really is mid-30s.

SHANE HUNTINGTON
Does it fall into that same progressive scenario that you find with Alzheimer's, which is incredibly progressive in some people? Does schizophrenia follow the same rules?

BRIAN DEAN
I think it's important to know that schizophrenia is what we call a syndrome. It's a series of disorders. Some people who get schizophrenia, oddly enough, will spontaneously remit and get better. Another group of people who get schizophrenia will actually do quite well during the rest of their lives, manage their illness. But there is another group which have this chronic form of the disease which is a little bit like Alzheimer's. They get worse and worse as life goes on and often finish up being
institutionalised for very long periods of time.

SHANE HUNTINGTON
This is obviously a very complex disorder. How do we go about investigating this disorder in a research sense given the complexity surrounding it?

BRIAN DEAN
Being frank, my view is we have to throw everything we have at this disorder. More and more people like myself are beginning to use the central platform of studying human brain, particularly brains from people who have had the disorder. Now we can do that in two ways. One's clearly neuroimaging and the big advantage of that is you can do it in living people, but it has a limited application. Then you can do what we do which is actually study post mortem brains. So brain taken at autopsy and there of course we can use a whole raft of molecular biological techniques we have to try and understand what's gone wrong in the brains of people with schizophrenia.

SHANE HUNTINGTON
When you look at the brain of suffers of certain disorders, there are marked physical changes. Do you see those in the case of schizophrenia?

BRIAN DEAN
You can go down to the level of looking at cells in the brain and no one can tell you someone has schizophrenia. Which is why more and more people like myself believe it's a disease of the molecular structure of the brain. That's my focus. Others are still looking at have they lost cells, have they gained cells? There's no convincing evidence there's any major change as you see in Huntington's, Parkinson's or Alzheimer's disease.

SHANE HUNTINGTON
When we go down to that very small cellular level, do we see any differences? Are there changes in the way the connections between neurons are made? Anything of that type?

BRIAN DEAN
No. No, again we work below the level of the cell. Once you start looking at levels at proteins, messenger RNA gene expression, you can see quite marked differences. Above that it's very difficult to see anything.

SHANE HUNTINGTON
What about when you look at something like functional magnetic resonance imaging systems where you can look at a living patient, watch the way they're thinking, watch the way they react to certain stimuli. Does that give any insights into schizophrenia?

BRIAN DEAN
It certainly does. That tells us the areas of the brain that aren't working properly. Because MRI is an interesting phenomenon in the sense it does give some information, not just on the size of the brain but how it's functioning. We've just for
example done a study with Dr Chris Pantelis at the university who is our star neuroimager. We're showing quite interesting changes in the brain of people with schizophrenia. But we've related that back to a genetic mutation in the gene we're interested in.

SHANE HUNTINGTON
I know when you put a person into one of these functional MRI machines you're able to look at things like their reaction to certain objects and so forth. Has a schizophrenic ever been put into a machine during a case where they're having a delusion or a hallucination? Does that show up in the same way it would for one of the rest of the population who just sees an object?

BRIAN DEAN
There are studies where a person with schizophrenia has been put into one of these machines and asked to press a button when they begin hallucinating. Then they do MRIs before and after. You do see areas of the brain that light up during that process, which is interestingly enough not the primary visual or primary auditory cortices which is what you and would light up if we see something or hear something.

SHANE HUNTINGTON
Interesting question there for a schizophrenic to push a button when they know they're hallucinating. Is it that clear to some of these people that that is occurring or is it a learned scenario?

BRIAN DEAN
I think it's more about these are people who are beginning to understand their disorder more and are doing quite well. So yes, they can identify when they are actually hallucinating. I think if you had somebody who is really sick then they wouldn't be able to differentiate between hallucinations and real life.

SHANE HUNTINGTON
You're listening to Up Close. Today we are talking about schizophrenia with molecular biologist Professor Brian Dean. I'm Shane Huntington. Brian how well does the brain of a cadaver retain the type of information that you need to do these sorts of studies? So the sort of information that you would be able to see in a living patient if you were able to dissect the brain for example.

BRIAN DEAN
A lot of the things that go on in our brain that need a lot of energy are lost, because we can't maintain the energy within the stores within the brain we collect. But there are things you can do at the level of looking at levels of messenger RNA and protein. Proteins are the functional building blocks of the brain where you can see things are increased or decreased. We've actually done an experiment which was quite interesting. I was surprised we could do it. We actually looked at the ability of one protein to bind to another protein in the brain of people with schizophrenia. The brain still has some molecular functionality to it, but it's very, very limited.
SHANE HUNTINGTON
Are you able to look at things like the thought processes that are going on during the person's life? Is there any recording of that, the psychosis moments, is that retained at all?

BRIAN DEAN
No, no. Well it's hard to tell, because how do you link a change in a molecular structure to what was happening in the brain when that person was alive. That's in the end what we might be able to do when we translate our studies into the neuroimaging machines.

SHANE HUNTINGTON
Brian, you obviously start off with a whole brain when you are lucky enough to get access to one. Talk us through what happens from that point? Is this a slicing up or are you looking at it as an intact specimen? How do you go about it?

BRIAN DEAN
We have been particularly interested in the molecular structure of the brain and what we found was that the way to preserve that is to actually process the brain very quickly. What we do is we slice the brain in a very organised way and then those brain slices are actually frozen very, very quickly to minus 80 degrees C where they are stored. They're quite stable for decades.

SHANE HUNTINGTON
Now I understand a particular group of receptors called muscarinic receptors have some relevance to schizophrenia. Tell us how they differ from other receptors and why they're important.

BRIAN DEAN
To put all this in context, the muscarinic receptors make up a signalling system in the brain called the cholinergic system which is driven by acetylcholine. This system is particularly important in maintaining cognition and therefore because people with schizophrenia have cognitive deficits, we've always thought it's particularly important in maintaining cognition. The muscarinic receptor is one path by which these acetylcholine can transfer messages around the brain. What we've shown repeatedly in people with schizophrenia is that they have lower levels of these muscarinic receptors and therefore this would impede the ability of messages to flow round the brain, in particular in the cortex which is the outer layer of the brain where we're pretty certain that area of the brain is very severely affected by schizophrenia.

SHANE HUNTINGTON
Presumably this opens up a series of pathways for pharmaceuticals to take effect in these particular patients?

BRIAN DEAN
This is a very, very hot area in the pharmaceutical companies. What we've discovered about muscarinic receptors is there is a number of sites on these
receptors that behave like the benzodiazepine binding site on the GABAA receptor. You can get at them with drugs and you can do amazing things with them to make the receptor work differently. It looks like some of these drugs called allosteric modulators actually may be very, very useful in treating schizophrenia.

SHANE HUNTINGTON
When you look at these particular receptors in the laboratory, how do you go about determining how they're functioning? Are you able to actually actuate them and make them do things or is it a chemical examination of the receptor?

BRIAN DEAN
It's a chemical. What we look at for example is the first step in these receptors to activate. If you can imagine these receptors are in the aerial on your roof and they have to send a signal down to your television set, the first step in that process within the cells of our brain is for the receptor to recruit a thing called a G protein. We can actually measure how well these receptors recruit G proteins in our brain tissue. In a subgroup of people with schizophrenia, we've actually shown that that's abnormal.

SHANE HUNTINGTON
When you consider some of the pharmaceutical treatments that have been used over the years and you obviously have a certain number of donors who you are able to examine, have you found differences between those suffering from schizophrenia who have been on a range of drug combinations compared to those who are not?

BRIAN DEAN
That's a difficult question to answer because we're faced with the chicken and the egg scenario. Whereby we may identify that a group of people have a change that is associated with them having a drug more often. The question then becomes is that caused by the drug or was it the symptoms that had them given the drug? Now if we treat a rat with the same drugs, what we usually find is that change doesn't apply. I think more often than not what we're finding is that subsets of people with schizophrenia get treated in specific ways and that's probably because of the symptom presentation when they're alive.

SHANE HUNTINGTON
There are Brian of course a number of other neurotransmitters such as Dopamine and numerous others that have been implicated with schizophrenia over the years. Are all of these systems of communication interlinked and perturbed by schizophrenia or do some people have one system affected and other people have another system affected for example?

BRIAN DEAN
The human brain is so interactive, that once one system is affected, that will have flow on effects to many of the systems. For example, we know that the muscarinic receptors are particularly important in controlling glutamate. We know that glutamate is affected in people with schizophrenia as well. We have to unravel an incredibly complicated road map of how these things interact to actually get to the base causes
of the disease. That's going to take a long time.

SHANE HUNTINGTON
You work very much on brain tissue of deceased individuals. How does this link in with what's being done in the functional MRI studies? How does that sort of connect the dots as it were to give us a better understanding overall?

BRIAN DEAN
So this is going forward in two ways. It's exciting because at the moment we are working with a number of neuroimaging people to try and translate what we're finding from our post mortem tissue into living brain. The easiest interaction we have is not with MRI but with the functional neuroimaging such as the PET. Chris Rowe at the Austin Hospital which is here in Melbourne Victoria, he's using neuroimaging with positron emission tomography which is a PET machine for short. What that machine is able to do is measure positrons leaving our brain from a particular radioactive compound that we've injected in the person that will actually bind to the M1 receptors. In fact we can actually see levels of these receptors in the brains of living people with schizophrenia. Actually see the molecules we're interested in. We're currently developing along with Chris a PET radioligand that will allow us to actually see muscarinic M1 receptors in the brain of living people. These are the receptors we've shown to be altered in the brains of post mortem tissue that we got from people with schizophrenia. That's the first step. With MRI what you can do, if you find a genetic mutation in a gene, you can ask the question is that genetic mutation associated with specific changes in the brains of people with schizophrenia? We've done that with Chris Pantelis. For example we've shown that a particular mutation in the M1 receptor seems to be associated with loss of cortex in a particular brain region in people with schizophrenia. There's multiple ways of doing it and we're now at a point in time where we have the technology, the ability and the desire to do it.

SHANE HUNTINGTON
Brian, what about the rest of the animal kingdom? Are we these sole holders of this terrible condition or do we see this in other primates as well?

BRIAN DEAN
When I first came into schizophrenia research from diabetes research I actually got a diagnostic manual and took it up to the zoo, Melbourne Zoo and asked the keepers there whether they saw anything vaguely like any of the psychiatric disorders we deal with? The one thing they could see was the equivalent of depression. They certainly couldn't see anything that would be like schizophrenia. But then the question they'd ask me would be how would they know whether a gorilla thought it was a fish? I think the nature of schizophrenia is too hard to define. My guess is probably not, because it looks like schizophrenia is driven by a part of the human brain which has evolved most from primates. I've written a review where I've argued the schizophrenia is a consequence of developing such a complicated brain.

SHANE HUNTINGTON
Many of our smaller rodent comrades on this planet have many of the receptors we
have. Does this still allow us to do a certain amount of animal model research as a result of those consistencies even though they may not end up being a schizophrenic or we may not be able to interrogate whether or not they are?

BRIAN DEAN
Absolutely. What we're now saying is that these animal models are not animal models of schizophrenia. They can be models of a component of the disorder. You can develop a model of a psychotic disorder driven by Dopamine or glutamate. We can even generate the equivalent of a negative symptom if you like by shutting down the cholinergic system in these animals. Then there's the next step which is of course modified genetic animals where we have mice in our animal house that we've taken the M4 receptor out of and we can see what this does to brain function. There's many ways we can use the animals to gain insight into what's going on in the brains of people with schizophrenia.

SHANE HUNTINGTON
How do we go and take the results of these studies you've been doing and change the way people are diagnosed and treated as a result?

BRIAN DEAN
What we're trying to do is translate changes into the brain into initially changes that we can measure in imaging machines such as the PET we talked about. But we're also trying to find molecules in the brain that have changed in the blood of people with schizophrenia. Because it's becoming more and more obvious that schizophrenia is not completely localised to the brain. There are things going on in the peripheral tissue and if we can find something that is a particular marker for something that's going on in the people with schizophrenia then we have a diagnostic tool.

SHANE HUNTINGTON
I'm Shane Huntington and you're listening to Up Close. In this episode we're talking about schizophrenia with brain researcher Professor Brian Dean. Brian do you believe that the number of people diagnosed at the moment is underdone? Is there a lot of people out there that are going undiagnosed and what percentage of our population have the condition?

BRIAN DEAN
I think that's probably not the case. It's not underdone. Because if you talk to psychiatrists, if you lock them in a room and throw away the key and you say don't talk about the diagnostic manuals they use, can you tell someone with schizophrenia when they come in the door? Invariably they say yes. They can't actually tell you how they do it, but they can say yes. I don't think there's going to be an explosion of people with schizophrenia and at the moment it seems to be everybody's beginning to agree that schizophrenia affects about 0.7 to one percent of the world's population. It's a huge problem around the world and interestingly enough it's gaining a lot of interest around the world as to how this disorder can be managed.
SHANE HUNTINGTON
Brian, when we consider things like our personal risk factors for ending up with something like schizophrenia, how do we know what they are? Are there genetic links here that might give us an insight or is this just something that we don't really know the causal factors for?

BRIAN DEAN
It's become very obvious recently that the propensity to get schizophrenia is genetic. It's got a high genetic load to it. However it's more complex than that. Because we now realise that there is certain environmental factors, we don't know what these are, that you have to encounter to trigger frank schizophrenia. That makes life very difficult. You may have a certain number of genes that increase your propensity for schizophrenia, but if you don't hit the environmental factors, you won't get the disorder. I think this is why we've had a lot of problems in making sense of all the big genetic studies that have been done. Added to the fact that it's a disorder of multiple small genetic input. So there's not one big gene mutation such as Huntington's chorea. On the other hand you could be more positive, because if you look at Huntington's chorea where we've identified the genetic abnormality we've come up with no cures, whereas in schizophrenia we've at least got treatments for the disorder that help about 30 per cent of people.

SHANE HUNTINGTON
Brian you mentioned some environmental factors being key to the development of schizophrenia regardless of genetic circumstances. Do we know what some of these environmental factors are at this point?

BRIAN DEAN
Unfortunately no. There is a growing amount of evidence that suggests in some people with schizophrenia exposure to stress to the mother, an illness or something in the third trimester might increase the risk. But there's no absolute findings that we could point to and often I raise the issue, this could finish up being something like if you have a genetic susceptibility for schizophrenia, do your university entrance exams a little bit later in life when you're more able to cope with them. Once we understand these, it's going to open up a whole new way of trying to manage schizophrenia, which will be really exciting I think.

SHANE HUNTINGTON
Are we at the stage where we can be tested for some of these genes or is it that's still a fair way off?

BRIAN DEAN
That's still a fair way off. They've done these huge genome wide association studies on 50,000 people and they've come up with two or three leads. But then it will take us probably 10 years to work through the biology of each of those and try to understand why they're precipitating for example psychosis or negative symptoms.

SHANE HUNTINGTON
When you're looking at a range of patients and you're looking at these particular muscarinic receptors, do you find the same conditions of those receptors in all patients or is there quite a range of scale of things that you find?

BRIAN DEAN
Actually no. We've actually made a really significant breakthrough which we published in the Journal of Molecular Psychiatry, in 2009 it was, where what we showed was that 25 per cent of people with schizophrenia have lost on average about 75 per cent of their muscarinic M1 receptors and actually form a distinct population, a subset within the syndrome of schizophrenia. This is really exciting because we've gone on from there to show that these people who have lost all these receptors seem to have a real problem in utilising their brain's energy stores. That would make them quite distinct from other people with schizophrenia. Oddly enough science is often cyclical because in the original brain imaging study's looking at energy utilisation, 25 per cent of people with schizophrenia showed up as not being able to use brain energy.

SHANE HUNTINGTON
You mentioned the word there lost with regards these receptors. What about the patients who seem to recover? Do we know what's happening at that point?

BRIAN DEAN
If anyone could find that out they'd certainly have made a Nobel Prize discovery. No one has any idea why this proportion - and we think it's about 20 per cent, just spontaneously get better. I've spoken to a number of clinicians. There's no predefining factors, there's no particular response to a drug treatment. There's something in there. Of course these would be a really interesting group of people to study. But obviously they're very difficult to catch.

SHANE HUNTINGTON
Brian I understand also that there is something of a link between people who have schizophrenia and the use of cigarettes, marijuana, a variety of self-medication techniques that may or may not be linked to the condition.

BRIAN DEAN
If we come back to the acetylcholine system that we spoke about earlier. The other family of receptors is known as the nicotinic receptors and that's because they buy nicotine and it's the active site for cigarette smoking. There are some studies that show that the nicotinic receptors are changed in the brain of schizophrenia. Similarly many years ago now we published a study showing that the receptor for cannabis in the brain is changed in people with schizophrenia. What may be happening here is that people with schizophrenia obviously get symptoms long before they come to a psychiatrist and get diagnosed. We know the lead time is five to seven years. Maybe in that time they're self-medicating with these drugs, getting some benefit. But then I think what goes wrong is that with time, particularly with cannabis for example, cannabis is now being shown to affect cognition very badly. It becomes a disadvantage to them to use those drugs. The real issue here is I think, drug taking
in schizophrenia could very well be linked to trying to self-medicate yourself early in the disorder and not really the same as other people who take drugs for other reasons. I think we need to recognise that. Interestingly enough one of the drugs that we use to treat schizophrenia, Clozapine, has now been shown to actually decrease the propensity of people with schizophrenia to take drugs. There's an interesting link there between later on in this disorder where effective treatment is beginning to reduce the drug taking.

**SHANE HUNTINGTON**

It's a very specific desire that's created obviously by the disease. Are there other similar things that you see in schizophrenics, not necessarily around drugs, but food, other requirements that have changed as a result of the disease?

**BRIAN DEAN**

It's very complicated to say. What I've heard from relatives is that one thing that changes and never comes back is their basic personality. You are getting a disease that's really going to the core of our personality and again if we could ever understand what creates our personality, if we understood those pathways, we may be directed to something to look at in schizophrenia. But again, that's way beyond our current knowledge. This is the real problem where we're really acting at high levels of function here that we haven't really fully understood how the brain makes these work.

**SHANE HUNTINGTON**

We've obviously been talking very much about the biological experiments, the research and so forth here. What about cognitive behavioural therapies? What role do they play in these patients and can they be effective in patients with schizophrenia in many cases, I assume, is quite severe?

**BRIAN DEAN**

Certainly listening to the clinicians I work with, yes cognitive behavioural therapy works. I think the reflection of that is it's used all around the world. I think that's the best judgement you can make about it. From talking to various people, I think it works in some people with schizophrenia. Oddly enough in some of the more severe forms, other treatments seem to have some effect. For example Chris Pantelis again who I mentioned earlier, talked to me before about they've introduced an art class with his treatment resistant people with schizophrenia and for the first time ever he saw two people with this severe schizophrenia leave their rooms, walk down the corridor to get to the art class. I think as with the research, everybody is trying to find ways of helping these people and you never know what's going to get a positive response from them.

**SHANE HUNTINGTON**

In the patients that do recover or at least go into remission from schizophrenia, does their personality revert?

**BRIAN DEAN**
No, apparently not. They're not the same person they were before they got the disorder. Clearly something in their brain has changed. The severe symptoms have gone away but again they don't seem to come back to be that person they were before the disorder set in. What that is will be some subtle change in brain neurochemistry, we really don't know.

SHANE HUNTINGTON
Brian, thank you very much for being our guest today on Up Close and talking with us about schizophrenia.

BRIAN DEAN
Thank you.

SHANE HUNTINGTON
That was Professor Brian Dean, senior research fellow at the Mental Health Research Institute and part of the Florey Institute of Neuroscience and Mental Health and Professor of Psychiatry here at the University of Melbourne. Relevant links, a full transcript and more info on this episode can be found on our website. Up Close is a production of the University of Melbourne, Australia. This episode was recorded on 21 August 2013. Producers for this episode were Eric van Bemmel, Peter Clark and Dr Dyani Lewis. Audio engineering by Gavin Nabauer. Up Close is created by Eric van Bemmel and Kelvin Param. I'm Dr Shane Huntington. Until next time, goodbye.

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