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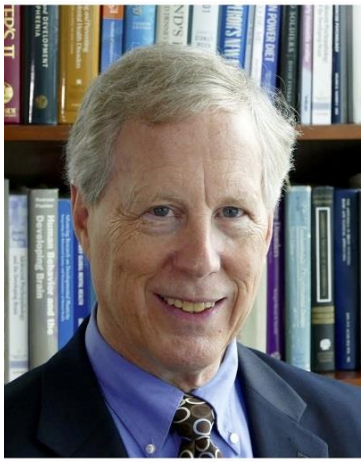
PRISM, RDoC, and neuropsychiatric diseases

Interview with Dr Bruce Cuthbert



Dr Bruce Cuthbert is head of the Research Domain Criteria (RDoC) Unit at the National Institute for Mental Health (NIMH) in Bethesda, Maryland, near Washington DC. RDoC is a research framework for investigating mental disorders. Its goal is to foster new research approaches that will lead to better diagnosis, prevention, intervention, and cures.

PRISM is a major European research project, funded under the Innovative Medicines Initiative (IMI),[1] to develop a quantitative biological approach to the understanding of neuropsychiatric diseases. By looking at the transdiagnostic symptomatologies that connect schizophrenia (SZ), Alzheimer's disease (AD), and major depression (MD) – including social dysfunction and certain cognitive deficits, such as attention, working memory and sensory processing – the project aims to identify the underlying biological features common across the diseases and open up possibilities for new, targeted treatments that operate irrespective of traditional diagnosis. ECNP also supports the project.

Dr Cuthbert recently spoke to ECNP press officer Tom Parkhill about RDoC, PRISM, and the future of research into the causes and treatment of mental health issues.

TP: Dr Cuthbert, thanks for talking to me today. Let's begin with a little bit about you. Where are you from, and what's your background?
BC: I'm from the state of Wisconsin originally. I did my graduate work at the University of Wisconsin-Madison and majored in both clinical psychology and psychophysiology. Back then it was a relatively novel field, to study simultaneous relationships between behaviour, thoughts, responses to stimuli and so on, and measuring physiological measures like brainwaves, eye blinks, and muscle tension. This was before the DSM-III came out, in the 1970s. I've always seen this as an advantage because we weren't channelled into these current diagnoses and thinking that we were looking at depression, an anxiety disorder, or schizophrenia. We were

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really looking at fundamental functions. We were studying emotion, and trying to ask, "how do we understand emotion?", not just in terms of feelings, but how do we measure all the various parameters? – like what people say, what they do, what their physiological responses are – and then to put that together in some kind of cohesive way. I think that was very helpful as I proceeded with my career. I would end up moving to the University of Florida for 17 years, to work with my mentor. We did a lot of research with a large lab looking at translation, considering emotions and measuring typical responses to pleasant or bad things, and then in terms of actual anxiety disorders.

We really had a translational lab. We had psychology students undergoing tests in the morning, and then we'd have anxiety patients in the afternoon undergoing the same tests, the same stimuli, trying to see how we could understand this in terms of people who have psychopathology.

You mentioned your mentor, who was that?
His name is Peter Lang. He's a very well-known figure in psychophysiology. He was the one who started the idea of the three-systems model of emotion. That is, if we want to be systematic and measure things in a true quantitative psychological fashion, we have to think about emotions as behaviours of various sorts. Then think about people's reports of how they are feeling – we can't measure these things directly; we can only see what people report. And then of course, physiological measures. So we try to put those three things together in a cohesive model.

What brought you to the NIMH?
After working at Florida for a long time I thought it might be time to try something different. We had had lots of conversations with the people at NIMH who administered our research grants. And so in 1998 I got the chance of a position at NIMH. I went up there first as a programme officer, helping administer research grants, and then I moved on up through the chain at NIMH over a number of years.

It sounds as if you had an ideal background for the RDoC work. Speaking to the PRISM people, they are very open about the debt they owe to the RDoC. Where did the ideas come from?
I'll give you a little background. Around 2005 I moved to the University of Minnesota. I had been frustrated by the lack of progress at the NIMH because applicants were mostly channelled by peer review to investigate the current DSM disorders, and there were no ways to grapple with the complexities. While I was at Minnesota, NIMH started to pull together its first comprehensive strategic plan for research, and one of the things that Tom Insel (the director at

the time) wanted to do was to implement some way of revising peer review for grant applications in more flexible ways -- thinking about more scientific approaches with respect to psychopathology. This was the idea that became RDoC, and I was completely unaware of it at that point. The staff were saying that we needed to look at basic functions and how they become dysregulated and dysfunctional. And those are part of what is involved with psychopathology; not to say that this is a single thing for a given disorder, but that we need to look at all of these different functions.

This all came out in the 2008 strategic plan. I just happened to come back for a meeting at Bethesda. I was chatting with Tom Insel and I remember telling him, "You know Tom, what you need to do is to look at these dimensional aspects which are involved with very basic functions". I had no idea that was exactly what they were thinking about at that time! Tom called up a few weeks later and asked me if I wanted "to come back for a sabbatical, to help us implement this?" I said yes, let's do it. When I got there it turned out that a leadership position was open for one of the divisions, so I came back in 2009, and started leading the RDoC project as well as leading the division efforts.

There were a number of people from throughout the institute – basic scientists, clinicians, etc, – all working to put this thing together. A real group effort.

It's very much applying science. Having worked for various societies in the past, for example in endocrinology, I am very conscious of having to balance the needs of the scientists and the needs of the clinicians. Here you are trying to introduce science into a very established and respected clinical domain. How did the clinicians take to this? Are they even aware of it?
Oh, they were aware of it, we published early on. It's important to say that the major reason we did this wasn't just to make a shift per se, but rather the fact that we couldn't manage to fund the kinds of research we thought was necessary. This was because the traditions had emerged (not through any requirement, just through the way groups work) that peer review committees who review clinical grant applications almost all agreed that what we study are the disorders as they exist in the manuals compared to healthy controls. Like I'm studying depression versus controls, schizophrenia versus controls, etc. There was really no way to say that we want to go and look at something very specific, like a specific aspect of schizophrenia. Or to compare how schizophrenia works compared to bipolar disorder. It was really a matter of point of view. So we had to provide a new framework, a framework for reviewing the more (if you will) forward-looking ideas on specific functions and how they work. That was the point: to enable a context for peer-review, to get different kinds of research going so we could get alternative perspectives on psychopathology. I think that's important. Many people in the field had been interested in this, and that was one of the reasons Tom Insel included this part of the

strategic plan. Many investigators were saying, “We need to do something about the DSM; it’s not working for what we are finding in genetics, brain activity”, and so forth.

So many were happy. At the same time, many were unhappy. I think a lot of that was due to unfortunate misapprehensions, that we were not sufficiently clear in getting this going. We had outlined different domains of function – like positive emotionality, negative emotionality, cognition, and so on – and then had workshops for each domain. Experts defined valid functional constructs based on the current literature; for example, cognition included attention, cognitive control, memory, language, etc. We also asked the experts to list measures of various data types that could be used to study a given construct. While all these elements were a basis for starting with well-known constructs, the main idea was that these were exemplars of how investigators could go about getting grants to generate their own new constructs. We were saying, “This is an example, this is the idea”. But that somehow didn’t get communicated. That meant that people were saying to us, “We really want to work with RDoC, but what I want to study is not listed in your domains”.

We also wanted to say that this was a research framework, it wasn’t designed to replace the DSM. But a lot of people felt that the aim was just that, to become the new manual. For us it was a long-term research project, to allow people to get used to the idea, to see what works and what doesn’t.

So the project started in 2008. How do you feel it’s going?
We put up the first funding opportunity announcements in 2011, with funding for 2012. I think it’s going well. In the early days there were a lot of people who were very excited. Gradually we started clearing up some of the misapprehensions. One thing which has made a big difference was Josh Gordon’s arrival in 2016. We started adopting computational models for how we can look at these things. From the start, we said that with RDoC we wanted to see people looking at analyses that integrate across these different kinds of measures – genetics, biology, behaviour, etc. But there were no really good methods to look at that. But when computational analyses and machine-learning came in that really helped things take off. We now have the capability to put the analyses together in understandable ways.

Which brings us to PRISM. What’s your relationship?
PRISM considered asking me to be on the board, but as a senior official at NIMH I need to make sure that there are no perceived conflicts of interest, so we couldn’t follow that through. I was very excited about the project. I ended up writing one of the original papers describing PRISM’s approach to study social withdrawal from an RDoC point of view – PRISM from the outset was oriented around RDoC principles, so I was very happy to write the paper. Since then

I have kept in touch. We were distressed to hear that there was some initial trouble getting refunding, but now that PRISM 2 is underway and going very well, they are really pushing into the computational models as well. They are using other innovative things, such as an app to look at digital measures, at how people are engaging with other people, how to measure social dysfunction in a quantitative way. We found this very interesting. In fact just last month I came back from a trip through Europe where I met Martien Kas and Hugh Marston to speak about PRISM and how it's going. I'm very excited about it. One of the most interesting points for me is that PRISM has been funded by the IMI, so it's not just a grant from a standard grant-awarding body, it's coming from a drug-development orientation, and I think that's very important.

It's especially interesting that they are looking at three such disparate disorders. Sometimes it's easy to, say, look at a transdiagnostic study with a specific phobia and social phobia, which are fairly close. But PRISM is looking at Schizophrenia, Alzheimer's disease, and major depression, and these are always considered very different diseases. But they are taking them on to see how we can understand the common mechanism for social dysfunction. It's not the only study like that, but it's one of the very few, and it's very innovative.

How should we be taking this project forward?
The international aspect is very important. The research in Europe is very well placed and is going forward on many fronts. I very much respect what the Europeans are doing, it's outstanding research in many ways. For one thing, the Europeans were amongst the leaders in developing computational models. Also, European groups have been looking at large cohorts, which the field can use to generate these machine-learning algorithms which require thousands of subjects to run a valid way. For instance, Peter Falkai in Germany is leading one of those right now. I think that's something which is really going to be applied internationally. In fact very recently we (at NIMH) published a somewhat similar funding opportunity written by the experts in our RDoC Unit: to recruit large cohorts of patients, probably in certain specific classes rather than a specific disorder, perhaps psychotic disorder, perhaps neurodevelopmental disorder, we don't know yet as peer review is pending. We will look at how we can get these large cohorts and do machine-learning analyses to understand how behavioural tasks and functions that we have implemented add to clinical records and clinical data, in order to see how much we can improve the identification of very specific clinical phenotypes that are more precise than our current psychiatric categories. We've been talking a lot to our European colleagues about how we can get these initiatives going.

Will you be coming to the European meetings this year?
Yes, I will be at the ECNP Congress. I'll also go to the New Frontiers Meeting, 'A roadmap for a

new diagnostic framework for mental disorders', in Nice, in March 2024. I'm actually on the programme committee, which was in fact the main subject of my chat with Martien Kas in Amsterdam last month. Martien, of course, is looking at potential treatment developments. He's interested in how we get those things approved by regulatory agencies. That's certainly something we will talk about in Nice: how can we shift the way that we set up clinical trials, what are the outcome measures, which groups should actually be studied to have more precision psychiatry cohorts where we can specifically target the problem? Instead of a broad syndrome, we'd have a very specific aspect that we can measure quantitatively and then target that with very precision treatments. I think that's where we are going in the future, but that's a problem right now because of the traditional models that everyone has had. This is not a fault. I'm not being critical of anyone; it's us as a field moving forward a step at a time until we see a little light at the end of the tunnel. I think that what's exciting, that after 40 years of stasis we are developing ways of moving forward. We're at an early stage, which is confusing but also exciting, but we can see this progress happening.

We do have to be patient with the situation we have now. We will need to continue for the foreseeable future with the kinds of assessment and treatment we know. At the same time, we need to think, "How can this change? How can we change our analyses, how should we interview patients?" As the science builds, rapidly, that change is feasible. This will take time, but we need to be thinking that a change will come. And that's happening.

TP: Thanks!

For the previous interview with PRISM co-lead Hugh Marston, see here.