Wellcome Trust Lecture 4 Questions
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Q: I'm surprised that the evidence is on the scientific validity of the results, the effects of incidental findings on the scientific validity of the results, because of course there are many sources biological variations in biomedical research studies and this is just another one, and this is why we have to use such large numbers, so I think it would seem unreasonable to do something which could, arguably be unethical just to make the science more robust.

A: Yes, it is surprising that if you do any medical research you select mice, with hair, without hair, with the same genes to have very homogenous population to ask the questions. It depends on the design of the study, but I think it's really prudent and careful to know what you are examining and how the brain looks like so I think this would be an advantage for the study.

Q: Lots of issues that you raised, but I just want to go back to something that was related to the last question there, which is the scientific validity argument. So if you take studies coming out of my lab there might be something like 20, in a standard normal study of BOLD activity. We heard earlier that the incidence of abnormal findings are about 1 in 37 (15% yes), but the idea that even at that frequency that it would invalidate the study in someway does not seem to be a very good argument because, as the previous questioner pointed out, there is a lot of normal variability anyway and the region you are looking at may not in any way be compromised and the probability that it is likely to be small, so it seems a very weak argument the scientific validity.

A: But this is your hypothesis, is there any proof, to which extent. For instance arachnoid cyst is a very common finding and the frequency is high, if you do functional MRI of the temporal lobe functions and there is hypoplasia of this part of the brain, to which extent is your results affected? You can just speculate but I think the possibility is there. You have to think about it and we have to study it.

Q: My view would be that the probability is extremely low, and I think the onus is not on me to show that it is compromised, it is on those who are putting forward the argument so show that that is the case.

A: The underlying problem is that in Neuroscience research we have still the 2 parties. So, on one hand you think that there is a soul independent from the organ (the brain) and that you will make soul research, and on the other hand there is the organ and I think we need to know what the individual organ looks like to better understand what you find out in terms of function and dysfunction.

Q: Just to follow up on that, research at my unit is doing things very similar to what Prof Dolan is talking about, but researchers would normally, if that information was available, often exclude one of their subjects for some reason, and it seems to me, I'm not sure if this is the ethical issue or if you should do this extra imaging on the one hand, but I think if that information is available, then it is very odd not to use it possibly as part of your exclusion criteria. People have got an outlying data point and if out of 20 subjects there is always

one outlier it's nice to have an independent reason to exclude that data if necessary, as apposed to going, "oh they just don't fit my curve".

A: I think it always depends on the research question and the hypothesis you are going to test but I think it would be a real advantage if, in the beginning before such a study participant is in the test situation, we have a clear description of the brain, and we don't run into all these problems with these echo-planar images and we see something and then we have to add on extra images and so on. So I think we have to come out this afternoon with a suggestion for a protocol which is sufficient to cover these problems.

Q: Comment following on from the points that have just been made.

I think it's important to keep separate the ethical issues about review of research imaging and those that might compromise the quality of data. But having said that, there are, and I review quite a lot of images that are used for fMRI, things that even outside the brain, eg. ossification of the falx etc, which would have a very marked effect of EPI based fMRI data, which is useful for the researchers to know about and may only be noticed by somebody who is actually reviewing the images from a Neuro-radiological or anatomical prospective. But I think these issues are separate from the ethical ones and I think we should be clear about that.

A: Bad science is also unethical I would say.

Q: I would like to shift the focus from research and whether it is valid or not, to the first point that was suggested by the German Society for Neuro-radiology, that in any case a neuro-radiologist should look at every scan, where as the Bonn Neuro-ethics group actually suggested that there was no necessity to look at every scan. So how is this actually reconciled within Germany, and part of the question is, is not the German Society for Neuro-radiology over emphasising it's own importance by suggesting that a neuro-radiologist should look at every scan?

A: I think that we were charged to develop guidelines as you are charged to develop guidelines. I think many radiologists examining the brain, these are neuro-radiologists in most German Universities, have a very broad experience regarding all these problems, all the facets of these surprising findings we have in clinical examination and also in neuro research and I think therefore we are in a good position and are charged to help to develop guidelines. The first suggestion was from this Bonn ethical group and this was our response, the first intention was to enhance discussion and to come to a common result. So therefore I said, I can not give you guidance here but just to describe the discordance we encounter so far in Germany.

Q: You have described a system with pre-screening by a Neuro-radiologist but I would be interested to know about the status quo. In what percentage of German research imaging institutes does that currently happen?

A: Only a few institutions, but there is a change. So as far as I can see, our ethical material will make this into a common requirement and we have a neuroimaging centre run by a psychologist and they have asked us to see every scan. But with a system for baseline diagnostic scan you need only one scan

for one study participant. If there is repeated imaging you don't need see every repeated scan. We have now a series of over 1000 we are looking at.

Q: You mentioned in several places the expectations of patients. Is there much actual published work, or other work on what the expectation of the German participant is in research studies, what do they expect to happen to their imaging?
A: There is no German paper on this, but I refer to the paper of Kershin often sited here, I think this is a very prease paper .

Q: The protocol you describe sounds laudable but how is it funded? It is quite radiology research intense.
A: This is one MRI examination and it's funded by the research money of the research groups. We are in discussion with the equivalent to the German MRC, and they discuss if you apply for a grant to implement this. And again, look into animal research. What amount of money is spent there to have clearly defined mice or rats and so on? So just to have additional information on our human research participants is better. The current situation is awful. You do liver imaging, you have a very limited sequence, it is not diagnostic, you cannot do a final diagnosis, you don't know what the question is that you are trying to answer. So the other way around, if you would have had a diagnostic abdominal MRI in advance. Knowing what the research question is then you could have avoided all these problems afterwards.

Comment: I should respond briefly to that and say we do dedicated MR related to the organ of interest, (ie and MR of the kidney or liver) but it's really not practical to do a whole body MR.
A: Then you should not do it, you should just examine the region which is examined during the research.

Q: Can I just take us back to the patient. You talk to the patient about the findings and leave it up to the patient to make the decision. At coffee break I was talking to a colleague who was talking about sending the information to a GP and then relying on the GP to inform the patient, and I just think we just need to also consider about how and what the ethics are about information transfer and who should be responsible for it. Would you like to comment from your German prospective?
A: The essence of this information comes from our image interpretation and therefore I think the Radiologist is in charge to explain the finding, what is necessary to do to make a diagnosis, what are the potential consequences, and also to add in a report that will go to the GP or specialist looking after this person putting it in context and saying what if any preference the person has already indicated . But you can not send the patient home and leave them to get a phone call from their GP and the GP has not understood what is on the image. So we are in charge.

Q: Following on from Tom's presentation today about what is actually happening in the UK and dividing practice into 4 categories of reactive/proactive and very proactive, I think what you've just described would go beyond very proactive because you are doing the extra imaging before the person is

actually put into the research study. And another thing that has come up this morning is that there are a number of different questions which there simply is no information about that you can use to make decisions on. I'm wondering if you are taking the opportunity, where you are trying to put this process into practice, to actually record what happens and to see what affect it has on things like workload and implications for research participants and things like that? Is there any comparative study going on where you can actually capture some information that would be really useful?

A: No, it is just my suggestion to do that.