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Title	*Languages disorders in children: What can they tell us about genes and brains?*
Description	Recent studies have shown that genes are strongly implicated in determining if children will develop language disorders. In this talk, Professor Bishop examines the role genetics play in language development and language disorders.
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Dorothy Bishop Well I think we may as well start ladies and gentlemen. First of all, welcome to Oxford, for those of you who are not inhabitants of this wonderful city. Thank you very much for coming along, on what's a gloriously sunny afternoon, you're cooped up inside, so I hope we will make it worth your while. My name is Dorothy Bishop and I'm a Professor of Developmental Neuropsychology here in the experimental psychology department in Oxford.

I was a student here many many years ago, back in the 1970s and I then trained as a clinical psychologist in London for a couple of years and subsequently did a doctorate here back in Oxford. I also worked for quite extended periods in the University of Newcastle upon Tyne and Manchester and Cambridge. Now I'm back again in Oxford, for about 10 years, funded by the Wellcome Trust, as a principal research fellow. It's a great pleasure to be here and to be able to show you some of the things we're doing in my research group and the sort of areas of research that have been possible to develop while I have been here.

So, I'm going to be talking about language disorders in children and first of all, I should point out, that this is really a Cinderella subject I think. One of the commonest reasons why people go to their General Practitioner with concerns about a preschool child, is that the child is not learning to talk on the approved timetable, if you like, of when they're expected to talk. Typically there is no obvious cause for this and in many cases it is, that the child is just a late starter and things sort themselves out, often it's not cause for concern.

There are children in whom these problems persist and can have long term adverse consequences. This condition, which is really very common and has been estimated to affect as many as 7-10% of children, is much less well known than say developmental dyslexia or autism. Despite being more common than autism and being closely allied with dyslexia.

You can do, what I call the taxi driver test, the taxi driver said, "Well, what do you do then?" You say, "I work on language impairments in children," "What's that?" they say, which you wouldn't get if you said dyslexia or autism. So, I'm going to try and redress the balance of it today and get you interested in this common but under researched disorder. Part of the problem is terminology, which is quite variable from place to place and country to country, but most of the people in the field, I think, have now settled on this term of specific language impairment.

Which is used to describe a child who presents with slow or disordered language development but where there's no obvious cause that you can detect. So, what you would typically do is to check

that the child hasn't got a hearing loss that could explain this, it't not part of a broader syndrome such as autism, it's not part of a general developmental delay and it's not caused by some physical abnormality that affects, for example, the ability to speak.

Typically these children are on a normal schedule of development in other areas, so they will be walking and looking after themselves and so on, on schedule for their age. Interestingly for those of us fascinated about how the brain learns language, there are some aspects of language that tend to give more problems than others. Having said that, these children can be really quite variable and you can't say that they're all the same.

The things that you most commonly see are these areas of problem, particularly when children are younger, there is difficultly with producing speech sounds. People often assume that this is something to do – they say, "Is it tongue tie," or something physical but it's not typically. It's more a problem in just learning to listen for the right things in what you're hearing and reproduce those sounds yourself.

Syntax is the other area that's often difficult, syntax includes both use of word order and use of inflections and things like case marking to express meanings. Word order isn't so often a problem but what you often see is, children who will omit inflectional endings and will perhaps use the wrong case. So, they might say, "Him go there," rather than, "He goes there."

Just to give you further example of the problem with phonology, if a child was telling you Goldilocks and The Three Bears story, they might stay, "Dodlock and the thee beard." Which is actually just a very immature way of saying that. You wouldn't worry about a two year old talking like that but if it gets to an older child who's still talking that way at age four, five, six, it starts to appear much more abnormal.

Then this grammatical difficulty I mentioned, so you get things like the child that says, "My brother like chocolate," rather than, "My brother likes chocolate." Omission of past tense endings, "Yesterday I walk to school," rather than, "Yesterday I walked to school." Or the same as I just mentioned, things like, "Him go to the park," rather than, "He goes to the park." They don't do this all the time, which is one of the most fascinating things, it's not that the child just can't put on inflections, a lot of the time they will use inflections appropriately but more often than you would expect another children you see these sorts of things.

So, I'm going to play you some examples, which I have to confess I had to download from YouTube because I was concerned about confidentiality issues with the children that we see, but they illustrate quite nicely some of these phenomena. This is a little girl, who is about four years of age and with luck we will see her trying to tell, not Goldilocks and The Three Bears, but The Three Little Pigs.

Right, I think I cut it off at that point, she does go at some length but she's very charming. In fact the comments on YouTube, quite a few people commented – they all said what a gorgeous child and several people said, "There's nothing wrong with this little girl." Which at one level they may well be right because she's still very young and talking like this when you are age three or four, we've found in studies, you may not look like most other three of four year olds but many children will start slowly and then do fine.

As I said before, if she's going to continue talking like this when she goes into school for example, then they're the children where we start to be concerned because typically they don't just catch up. There is a big variation in normal development, in terms of ages at mastering language but this certainly is late. Given that she is a very bright, valiant little girl in other respects, very sociable, it stands out as a specific problem. Now in her case, she did appear to have predominantly just problems with talking and getting her sentences right and getting her sounds right.

In some children the problems actually extend to understanding, as well as producing language and we can test that using tests that don't in fact involve any spoken, any requirement on the child to speak. So, this is the sort of thing we might ask a child to show us, 'The horse is pushed by the

girl,' to select it from this array. We will typically give them a number of items, testing different sorts of things and we know, from studies of typical children, what's reasonable to expect from children of different ages.

It's quite common to find that alongside problems with producing language, there may be problems with understanding language. The issues that I want to address today is, what we can understand about what causes SLI, what causes specific language impairment. There's a lot of answers that seem terribly obvious but turn out to be wrong. One that drives me insane, with the frequency with which she comes up in the media, is that it's that parents don't talk to their children.

Every few years some expert stands up and says, "We're facing an epidemic of language disorders in our children because parents have stopped talking to their children." This is just an instance from the media a few years ago, where we were told there was not enough talking, parents were grunting at their children and damaging their language development. Parking them in front of the television and that this was causing major problems.

The difficulty is, that this is described as research but actually it's typically people's opinions and there isn't good hard evidence that there has been any change or any epidemic of language disorders or any difficulty of that kind. There's evidence against it in fact, because if you want to test this idea you can start looking at children who develop adequate language, despite very variable levels of spoken language from their parents.

One way to do that, is just to see what happens in different cultures. There are cultures according to anthropological research, where it is really not regarded as a good idea to talk to young child and where it's more traditional to say, for example, strap your infant on your back. Basically leave them there, feed them and so on, but not really converse with them, not do all the things that we think of as terribly important to do with babies. These children seem to grow up okay and learn to talk, despite really having parents who think there's no point in talking to a child until they can talk back to you. (Laughter)

Perhaps also more interestingly, there are twin studies which show that there are cases where you get dizygotic twins, twins who are not identical, growing up in the same environment, growing up together in the same household and yet one of them has got specific language impairment and the other is entirely normal, in terms of their language. We also have the case of children with exceptional circumstances, including hearing children of deaf parents.

Child with receptive language disorders coming up we hope! So, this is his mom as well, it's not some person trying to do a test with him, really trying to tell them how to transform his act and he kept saying because something or other. At one point I think he said, "Ice cream." He didn't really seem to understand the question at all and that is a sort of quite extreme example of comprehension problems, where you really feel, what is it about it that he can't understand? You might think, "Is he deaf?" but apparently not, he's been tested and can hear okay.

So, this is really quite disturbing when you get a child who seems to have so much trouble understanding. What I want to contrast that with, is a much older child, this is a teenage boy but he is a boy growing up with two parents who themselves are profoundly congenitally deaf, who can principally sign. So, he gets a lot of signed language input, his parents are extremely communicative with them but what he doesn't hear is a lot of speech.

Children like this, when they - in about the 1970s when I started in this field, a lot of people were concerned that this could be very bad for them because they would not develop normal spoken language, if they were only exposed to sign language or not very easy to understand speech from their parents. The amazing thing was, that the few studies that were done suggested that this wasn't the case at all and that these children in general, were really developing okay, as you can see from this boy. So, these hearing children of deaf parents, okay.

So, I think this really challenged ideas, that the children need a lot of clear spoken language input at home, in order to develop normal spoken language themselves. Obviously this boy is getting spoken language input from the television, from people other than his parents and he's getting an awful lot of communicative input from his parents through sign language. It does seem that that is sufficient and so, it makes it much more unreasonable to think that some sort of grunting at your child and putting them in front of the television is enough to cause a serious language disorder.

So, the next thing that you might think this possibly implicated, is some kind of brain damage. This idea is a very old idea, it's been around really since about the 1950s. Again it makes a lot of sense but it turns out not to seem to work in this case. This was the idea that was advanced by the idea - that might be some sort of so called continuum of reproductive casualty, by which they meant that we know of cases where at the time of birth the child's brain is damaged because they are very premature and the brain bleeds, or because of anoxia or something like that.

We know that if you have severe cases like this, it can cause major problems in the child and obvious brain damage and numerological difficulties. The idea was suggested, that maybe smaller degrees of less obvious trauma, could perhaps cause milder things. Like the sort of learning difficulties that are involved in various specific learning difficulties, including specific language impairment. This slide just shows you a instance of intraventricular hemorrhage here.

That is a very common thing in very premature children, that you get some sort of bleeding into the brain, which you can see around the time that they are born but then subsequently it wouldn't be particularly obvious, for example, on a brain scan. So, you think well maybe this is the sort of thing that has been going on. However, there really have been a number of studies now, looking just at the birth histories of children with specific language impairment and they really seem rather unremarkable in most cases.

You are not seeing an excess of premature children or children who have had deprivation of oxygen or anything like that. Perhaps, again, the other interesting piece of evidence is, to it turn on its head and say, "Well, what about children who do have brain lesions, what happens to their language?" There is perhaps the most surprising piece of evidence because here is a picture of a brain from somebody who has, as you can see, has had half the brain removed.

A fairly dramatic procedure that you wouldn't undertake lightly but that is sometimes undertaken in childhood, where a child has a very serious malformation of the brain, that the course is chronic epilepsy. You're left with a child where the epilepsy itself is further damaging the brain and the drugs that they are given to control the epilepsy, are also causing a lot of problems. So, it can happen in these very unusual cases, that the decision is made that the best treatment is actually to remove half the brain.

You would've thought if you do that, that's going to be catastrophic for language learning but surprisingly enough it was shown, way back in the 1950s, with a whole series of children who'd had this procedure done, that it does not necessarily compromise language development, even if the left side is removed. We know that in most people, it is the left side of the brain that is most important for language functioning. This reflects the amazing plasticity of the brain as it's called, it is really just that it's not fixed at the time of birth, which bit of the brain is going to do what.

So, you can get reorganisation of the damaged brain, provided this happens early in life. So, what that starts to say to us is, well how come some of these children have got language problems, why don't their brain's reorganise? The answer seems to be, that they don't have any stimulus to reorganise because they're not actually damaged brains, there're brains that are just developing differently.

My colleague Christiana Leonard, who works at the University of Florida, is one of the people who's done the most studies of a range of learning disabilities, including language problems and said that when she started out in this field, she was doing neuroanatomical studies, staring at these brain scans of these children. She said that she expected to find holes in the brain, or something

that you could see because these were children that were really quite impaired. She said, that's not what they found.

What they found sometimes was just a rather unusual and atypical pattern in the brain, of the gyri and the sulci, the convulsions of the brain might look a little atypical but you couldn't say, "This is the brain of a dyslexic person," or, "This is the brain of somebody with specific language impairment." There is a lot of variations and certainly there was no one to one correspondence, between what you saw on the brain scan and what you saw in terms of the behaviour. This is an ongoing project, we have at the moment a collaborative project with her, to look at brain scans of some of the children that we're working with.

It's clear that there's much more variation between families, than there is within families, so that there is huge individual variation in brains, just as there is with things like faces, with a lot of family resemblance. It's actually proving very hard to pinpoint something distinctive about the brain of a child with SLI. We're also doing a study with my colleague in psychology, Kate Watkins, who's an expert on brain scanning with children. Where we have got, not just the children with SLI but their siblings and their parents.

We try and get the entire family into a brain scanner, which is no mean feat, it takes most of the day, but we again find no gross differences. You could look at these brains, even somebody who's quite experienced at looking at brains such as Kate, would not be able to say whether this is the brain of a child with specific language impairment or a control brain, just from looking at it. Which is in some ways reassuring, I think, for the parents of children who have these problems.

What we do start to see, and this is still a project underway, but there seems to be evidence that what we are seeing is rather more subtle differences in the distribution of gray matter, in different regions of the brain, including the language areas. If we actually do scanning while somebody is doing a task, so we can look at how the brain metabolism changes as you do a language task, we can show that there is less activation in language areas from people who've got language problems.

Although at one level you could say, maybe that's not surprising, they've got language problems, they showed less language activation. It's not sure whether we're measuring cause or effect of their problems. The structural differences are there but they are very subtle and so we are currently looking - also we are pursuing this line of work. We're also interested in the idea that, maybe the connections between different brain regions are what are different, rather than there being, again, this sort of notion of holes in the head.

Overall I would say that we can sum up by saying, that the evidence points to fairly subtle problems with early neurodevelopment and connectivity between different brain regions, rather than brain damage in these children. So, that then raises the question; how do we get there, why do these children have these problems? The answer would appear to be that, you're likely to have some sort of genetic basis for these disorders, rather than something that is acquired, not necessarily followed, but is clearly a line to peruse.

It certainly converges with other lines of evidence suggesting that genes may be implicated. So, I'll move on now to say something about work on genetics in this area. So, many years ago, well 1980s, there were these studies done. A number of studies, three in the states, one by me in the UK, where we were just taking groups of children with language impairments and a control group of similar social background, and counting the number of relatives that they had who had similar problems.

I did this as part of a much broader study, I was studying a large group of children when I was up to the northeast of England and I really had a questionnaire that asked almost everything you could possibly imagine, including their birth histories, their illness that they'd had, aspects of the home environment, etc. etc. It included this question about, anybody else in the family having problems and this was the one question that differentiated the groups.

So, it was the case that you had about 24% of relatives of children with SLI, had some sort of speech and language problems themselves, whereas it was only about 3% in the control group. As you can see, these other studies done in the States, the differential there in every one. The absolute levels tend to vary but I think that's largely just because people vary in the criteria that they adopt, for deciding whether or not you've got a problem.

So, that starts to suggest, it's at least compatible with the idea that genes might be implicated. Then you could say, "Well, it's not compelling because families share a lot of things, other than their genes. Their nutrition, their living circumstances, all sorts of other things could be involved." So, you really want to be move to a situation where you can start separating out genetic and environmental influences. Fortunately we have this method, that's been around for many, many years that starts to give us a handle on the separation. That is to start studying twins.

People in this area love twins because they're a natural experiment that's just out there waiting to be capitalised on because nature has provided us with two types of twin. We have got monozygotic twins, who are genetically identical, or nearly so. There are debates about whether they are really identical but they are certainly made by the splitting of a single fertilised egg and so about as identical as you can get. They're the ones that look identical. So, then we have the dizygotic twins, who are like any other brother and sister pair and so they are more similar than random members of the general population but they are not as similar as these guys.

To put it officially, they share on average 50% of their polymorphic genes and I found that this really does need explaining because it confused me for years, that people would say, "Well, brothers and sisters have on average 50% of their genes in common." Then somebody would come and say, "Humans have got 98% of their genes in common with a chimpanzee." I thought, "There is something wrong here!" (Laughter)

Indeed I think somebody worked out that we share something like 40% of our genes with a daffodil! (Laughter) So what does this mean? Well what it means is, that there are two sorts of genes basically, there are genes that take the same form in everybody. They're so important for building bodies and bits of bodies, that if you get a mutation you typically would die and so we all have exactly the same form. Now genes like that can't possibly explain individual differences between people because we're all the same.

So, it's only a small proportion of the genome where the genes vary from one person to another and you can have slightly different sequences of DNA, depending on who you are. Those are the ones that we call polymorphic and that's the only bit of the genome that geneticists like me, or I'm not a geneticist, but geneticists and people like me would prefer to, when they say about this 50% figure. 50% are the ones that do vary, so that makes much more sense in the context of the chimpanzee.

Now twins are interesting because, when you say to people you work with twins, they say, "It must be very hard to find these twins that are separated at birth." I don't even begin to try to do that! We study twins who are growing up together in regular situations but the interesting thing is, you can still learn a lot from twins who have grown up together. You're going to expect them to be similar, any pair of twins, because they share a lot of environmental factors.

So, that will make - if you've got the same sort of television watching parents, who grunt at you and dump you in front of the television, or parents who are very concerned about making sure you get lots of linguistic stimulation, that's likely to affect the two twins growing up together. So, twins are expected to be similar but the interest is in the difference in similarity for the monozygotic and dizygotic, because if one group is more similar to each other than the other, that does start to suggest it's genes that are important.

Particularly if you focus attention just on the same sex ones because otherwise you get confounded with sex differences. So, the same sex ones all dizygotic, so we just look at same sex dizygotic versus monozygotic. I won't bore you with details of the more sort of mathematical and statistical

analyses that you can do to get out estimates of genetic influence, which I'll have a reference list available on the web if people want to pursue that. The bottom line really, the most important thing to remember is, that that is the logic of the method.

You really just say, you have pairs of monozygotic and pairs of dizygotic twins and say, you expect them to be similar twin-twin pairs. Are they more similar if they are monozygotic? In general that has been found to be the case, so for a long time there were just these three studies published in the 1990s and in each of those first three cases, you can see there is quite a higher number here. That's a measure known as `[[pro ban wide concorn 0:25:52]]`, which is the proportion of affected twins, who have an affected co-twin with SLI.

You can see that this number is bigger than that, this is bigger than that, etc. So, all of those are pointing to genetic influence and then along comes this study in 2005, to make it worse it was done by an ex-research student of mine, particularly irritating! Which showed no difference at all, between the monozygotic and dizygotic and in fact found very low twin-twin similarity in both groups. Interesting psychological phenomenon, I suppressed this for quite a long time, I just forgot about this result and it just didn't fit into my mental model, and then I was forced to do a literature review and I came across it and I thought we really had to try and explain this.

Fortunately, we were able to do so in a very interesting way. The difference between this study and these three, is that these three all used a fairly clinical definition of language impairment. So, these were children whose parents had sought some sort of help for their child's problems. These were children from a general population survey, where their parents had simply been asked to estimate their vocabulary size with various checklists. They were not - the ones who are at the bottom, and who were deemed to have problems, were not necessarily receiving any clinical services or their parents have might not have sought them.

What I suggested to Emma `[[Thomas 0:27:13]]`, was that we should look at - we had the information on whether they had sought clinical services and would that make any difference? It made a huge difference, we suddenly got back to the territory I was familiar with. A nice big difference between the two groups. So, this is just defining specific language impairment, in terms of whether you've sought clinical assistance.

Why do you seek clinical assistance, is the next question? The answer seemed to be, when we looked at the characteristics of these children, it comes back to these problems with speaking. So, you can have rather poor language skills but if when you open your mouth to talk you don't sound odd and you're fairly easy to understand, people don't tend to worry about you. Whereas if every time you open your mouth, people are trying to work out what is it that you said, then people are much more worried.

So, it does seem that these early, what we would call phonological problems, problems in producing the speech sounds, might be pretty key in identifying what are the types of problems that are more genetic in origin. It just emphasises how careful you have to be as well and how a slight change in a definition can make a big difference to what you find. So, there's evidence for this fairly substantial genetic influence on SLI but there's lots of remaining questions, including, "Well, is a gene there just a gene that we can identify for SLI?"

We know there are genes for other conditions, is there the SLI gene or is there perhaps, not one SLI gene but lots of them? Maybe this whole group of different conditions but we can find a gene for each one. What I'm going to argue is that, unfortunately life is not so simple but I'll show you the evidence first of all. So, here's the evidence that looked first of all very promising. This is a family that's actually very well known in the literature because they were so impressive, in terms of providing evidence for a single gene disorder that causes speech and language problems.

They are known as the 'KE' family. They've been reported by various researchers, who all disagree about what's wrong with them, to such an extent that when I visited America, people thought they were different families being described. Thought we had a lot of these families in

Britain because people don't tend to cross reference each other. Basically, what you see here is a family tree, so these are males, these are females. Females are nice and round, males are sort of square.

If you're coloured in red, you've got a severe speech and language problem. As you can see, there's an affected grandmother who had five children and each of these, this is a geneticist's dream family because they had such a lot of children! You can see though, just by eyeballing it, that it seems to be about - if you've got an affected parent, you've got about a 50% chance of being affected yourself. This is what you would call a classic mendelian pattern of inheritance, it's equally likely in the males and females.

So, it seems to be on one of the autosome's, not on the sex chromosomes but it suggests that there must be a gene that is mutated in this family, that's causing this problem. Indeed such a gene has been found. So, this work was done up the road, up the hill in Oxford by a colleague, Tony Monaco and his team. They were able to find this gene, known as FOXP2, which is on chromosome seven which doesn't vary in the general population.

It's one of these genes that's not normally polymorphic but in this family, the affected people all had a mutation of just one single base in the DNA sequence. So, everybody got very interested in FOXP2. What does it do, where does it come from? There was some very interesting work done comparing it across different species. This is a gene that is evident, not just in man but in mouse and in primates, and the differences between man and mouse are really very slight.

The differences between man and chimp affect two amino acid positions, so this interested people because they said, "Well, basically most of the change in this gene, which is arbitrary mutations, which don't compromise survival and allow you to continue. Most of this occurred after the separation from chimpanzees and it suggests that there might be some selective advantage to the change, that happened between chimpanzees and man."

So, everybody got very excited. Was this the gene for language or at least the gene for grammar? The people who have done the work on this gene all say, "Absolutely not, we should put this idea right out of our minds, it's far too simple minded," because it's not a gene of a simple kind. It's known as a transcription factor, it regulates the expression of other genes and it is expressed in many, many organs. In the kidneys, in the heart and heaven knows where, but in the brain as well. It's really not a gene that is really specific, in any way, to language.

Furthermore the affected members of the family appeared to have some other problems beyond grammer, although less than you might thought, given its role as a transcription factor. The argument has been put forward that really this is a gene which affects bits of the brain that are important for movement, for motor control and that that is why these people have speech and language problems.

Nevertheless I would say, that in itself, might also turn out to be too simple because these people do have trouble with some of these comprehension tests, that I mentioned earlier. So, its been documented for example, if you give them this sort of sentence, which is a bit fiendish, "The elephant pushing the boy is big," because you've deliberately put the big next to the boy, who isn't big, rather than the elephants. To decompose that you have to extract some hierarchical structure whereby that's all one element, and that describes that element.

This is the sort of sentence that children with SLI have trouble with. These members of the 'KE' family also had evidence of trouble with. So, I think they may have some additional rather more specific linguistic problems, that aren't just explicable in terms of speech production. Nevertheless, I think it's reasonable to say that FOXP2 shouldn't be seen of as a grammer gene or something of that kind. It is much more complex than that but it might be that amongst its many roles, it does help build a brain that can do those sorts of linguistic operations, but it's clearly not a gene that only does that.

So, that's my stance on that, although it is still very much a matter of a lot of debate between people. Is it the explanation for SLI? Of course that was my interest, is that we might have now found the gene for SLI. We immediately found out that no, it wasn't. This it the exception rather than the rule, Tony Monaco's team and other teams elsewhere in the world, have taken larger groups of children and families where there is SLI and failed to find any evidence of any mutation of this gene.

A few other cases have been found of the mutation, associated with speech and language problems but that is after a very comprehensive search and it's a tiny, tiny minority of the population with language problems. Also, if you look at the family trees of the sort of children I work with, they don't look anything like as straightforward as that 'KE' family tree, in the majority of cases.

So, what you find is this increase in other family members affected but you can't really trace it through and say, "Ah, yes. We can see it coming down this line of the family." Unfortunately what that tends to mean is, this is what's known as a complex multifactorial disorder. Where, although aggregates in families, that is you get a higher rate within a family, it doesn't segregate. You can't, sort of, see this gene going through the generations, according to any sort of simple rules.

Unfortunately this is how many, many disorders in medicine work and it looks as if a lot of our common developmental disorders fit this pattern. That they're not caused by one particular thing. In fact its been argued that that is partly why they are so common, if there was a single gene that made you unable to communicate, it's likely it wouldn't have survived in the population over the years because you would be at a disadvantage relative to other people. So, what seems to survive are lots of genes that have small contributory effects but which act together in a fairly complicated way.

Just as we know is the case for things like heart disease and diabetes. So, the idea was that we have a whole distribution of abilities in language and individual genes have small effects on any one underlying skill. You add it together and you pretty well have a normal distribution, which also explains why we have real difficulties with conditions like SLI, deciding where to put the cut-off between having a problem and not, but it genuinely is quite continuous.

The question then is, how are we going to discover the gene? So, we think there are genes involved because these things run so strongly in families, but how are we going to find them if they're all rather small genes that don't have much effect? The approach that I have favoured is to say, "Well, let's take a step back and perhaps stop looking specifically at SLI, as it's clinically diagnosed as either present or absent, but let's try and look at some of the underlying factors that we think are involved in causing SLI. The sort of linguistic and perceptual and cognitive things that seem to compromise language learning."

Can we find genes that are involved in them? This is an approach that's very analogous to what often happens for physical disorders, where people try to find what they call an endophenotype, by which they mean some sort of physiological change that's correlated with the disorder. Instead of looking for something physiological, I would argue that we can also do this as psychologists looking at more cognitive things. What are the sorts of things I mean?

Well, there are a number of theories around, that been around for some years about underlying factors that might cause SLI, and that's a good place to start. I won't go into detail about these theories, one could give an entire hour long presentation about any one of these but just to say, that they are rather differential types of theory of SLI. The first one of which suggests that's a secondary consequence to some sort of auditory problem. The second of which, attributes it to short term memory problems of a particular kind. The third which says, no it's actually something more specific to the linguistic system.

So, I'll just give you a little bit of information on this. The auditory repetition test, is a test which we use to measure this auditory processing problems that's been proposed by a very influential psychologist called Paula Tallow. Paula Tallow argued these children aren't deaf, we know that

they can hear sounds, they can detect sounds but what they might have difficulty doing is telling sounds apart, particularly if they are rather brief or very rapid. She has had a whole research career attempting to evaluate that idea.

In conjunction with her, I was involved in a study where we tried some of her measures of auditory processing with twins. So, the sort of thing the child is asked to do is, they're first of all trained to listen for a high tone or a low tone and to press one button for a high tone and one for a low tone. When you're confident that they can do that, you start seeing if they can press the buttons to represent tone sequences. So, this is the sort of thing that they would have to listen to. (Tone noise) That's an easy one but this is a hard one. (Tone noise)

You can vary the length and you can vary the speed and both of those make it harder. We knew from prior work, that a test like this is something that children with SLI do find harder, than matched control children. Tallow has built up a whole theory that this is underlying difficulties they have with language learning. They don't really have, according to her, a linguistic problem, they have a problem in perceiving sound, which leads onto language difficulties.

That's rather different from the next type of theory which says, actually the difficulty is one with a memory system that humans seem to have evolved for language learning. Which allows us to hear a sequence of speech sounds and immediately retain it for a brief period of time. Which is a sort of skill you need for learning the name of someone you've not heard before, or learning another word.

It's a very simple test that you use to evaluate this, you give them things like, "`[[Hampent″ 0:39:47]]`. You say, "Hampent," and the child has to repeat, "Hampent." Or, "`[[Doppilate 0:39:52]]`." Again, you can increase the length, that seems to be a factor that particularly gives children difficulty. You might say, "`[[Confrancktually 0:39:59]]`," or, "`[[Pristaraction 0:40:00]]`." They are things that sounds like words but are unfamiliar to the child.

This, again, has been shown to be quite a sensitive test to specific language impairment, children with SLI have difficulty. Now you might say the children that you have seen on the videos wouldn't be able to say this anyway because they've got such a lot of problems in speech production but interesting thing is, that you find that this is typically used with rather older children who have overcome those problems with speech production. What you find is, that even though they can produce the sounds in isolation, they have a lot of difficulty producing these long sequences.

It's thought to be more of a problem with remembering them, than physically getting your mouth around them. Then the third type of test that we used, was one that emphasises these problems with grammatical morphology that children have, where they just seem to have these difficulties putting on past tense endings. So, you give the child little pictures and this is material that I was sent by Mabel Rice, who works in the US, who kindly let me have access to a test materials before they were published. You say things like, "Here the boys raking now, tell me what he did?"

The child is given some practice items and trained to say things like, "He raked leaves," you're listening for that past tense ending and then there is a third person singular analogue. "Here is a farmer, tell me what a farmer does?" The child might say, "Well, he feeds the pig," or he might say, "He feed the pig." If they live in the country they might say, "He killed a pig." You don't really mind what verb they use, what you're listening for is the third person singular ending, that S on the end, which is left off quite frequently by children with SLI.

Now, I won't go, through the interest of time, into all the data we have on this because this work is all written up but the conclusions from using these different measures turned out to be really rather fascinating. The different tasks all behave differently and I was rather amazed by this because it's not why would've expected. I should say, I'm summarising results from two separate studies here.

It would have been nice to do a single study with the same children on all measures, but this has evolved over time.

So, there are two sets of twins samples which are incorporated here but essentially on that auditory task with the beeps, we found that twins resembled each other quite closely but it didn't make any difference whether they were monozygotic or dizygotic. They tended to just be similar to one another and that points to an environmental influence on this skill. In fact we found it correlated to some extent with musical experience in the home, which we just asked what parents about in a questionnaire. Perhaps not so surprising.

We actually didn't find any evidence that is was picking up any kind of genetic problem. This is quite different from the phonological short term memory, where we found quite striking differences in similarities. Monozygotic twins, if one had a problem with that repeating long words, the other had a problem. Dizygotic twins, it could go one way or another. You just found this closer similarity and it translated when you get the sums, into a really very strong genetic effect on this particular task. More for syntax, was also coming out as a very strong genetic effect, also for the monozygotic twins more similar than dizygotic twins.

I thought, well it might be that there are really just different measures of the same thing. Maybe if you can't remember sounds then you don't learn to put the past tense endings on, but in fact we can check that out by looking across these two and saying if we've got one twin that's bad at this, is the other twin bad at this? You can really treat them, do they act as proxies for one another? They didn't at alls, they were not very strongly correlated. So, it was rather more interesting and suggested we have these different factors that can compromise your language development but which have rather different underlying causes.

Furthermore, we found that if we then looked to which of these children had actually going to receive a clinical diagnosis, the more of these problems you had, the more likely you were to be diagnosed with SLI. So, although these disorders were, we feel distinct in terms of their underlying causes, obviously some children would have a constellation of problems. It was these poor little ones in the middle, who were typically struggling most. Perhaps not surprisingly at one level, but it suggested to us that we really should not try to think of 'The Cause' of these disorders but be aware that it seems to result from a constellation of quite common problems.

That's what really this slide says, that different deficits may have different underlying causes but the impact on language is really when you get different things co-occuring, different risk factors. So, I just want to close by saying a little bit about colleagues of mine in the Wellcome Trust Centre for Human Genetics, who've taken this further, to try and identify the genes that are underlying all of this. I'm not a molecular geneticist and I couldn't possibly do this work, but I have the good fortune to be working in Oxford, where we really do have a stellar group of geneticist's just up the hill.

They are not just stellar but they are also highly collaborative and we've over the years forged a really useful collaboration, where psychologists and geneticist's make extreme efforts to communicate with one another. I think this is probably unique in the world, to have the degree of interaction between two disciplines that we have here. I'm delighted that my colleagues, Diane Newbury, Simon Fisher and Tony Monaco are here and are people that I can work with. It has been enormous fun.

So, just to say little bit about what's happened over many years of painstaking work, they do studies where they get large groups of people and their relatives, who have SLI, and start looking for genetic similarities and differences between them, at the level of analyzing DNA. They've found three, what they would call genetic variants, so three bits of DNA where it can vary. These sort of polymorphic regions, that are associated with how well or poorly you do on long word repetition in SLI.

Because there is such a lot of DNA that you can potentially look at, you have to be fairly scrupulous about checking your findings and replicating them, before you take them seriously. This group is very good at doing that. They don't get overexcited until they're fairly confident that they can show this in more than one sample. They found two and published earlier this year, two genes on chromosome 16, that appeared to act additively and which effect performance on long word repetition.

Interestingly they found the third gene, which is downstream target of FOXP2. So, it seems to be on the same pathway, it's not FOXP2 but it would seem to be part of the same biological pathway, which makes a lot of sense. They've got one set of results on associating poor performance on verb morphology and it's on a different gene, on a different chromosome. Which would fit with the behavioural data suggesting that there are genetic effects on this but they are not the same.

This is just to show you the data on these two genes, that were published earlier this year, a figure from Diane Newbury. The interesting thing about this is that it's so different from what you see with FOXP2. If you have a FOXP2 mutation, A, it's very unusual, you wouldn't see it in the usual population and B, t has a really big effect, it really knocks down your language and speech performance.

These are common in the general population, these are really just thinks that you may find 40% of people have got this risk version, it might not be as high as that, 20%, 10%. Lots of people in this room have probably got the risk genes and what they're associated with is, not a dramatic deficit, this is a change if you've got the non-risk form, scale score of 94 to 88. Those of you into standard deviations, that's about 15 points as a standard deviation, it's about half the standard deviation also. Not massive and indeed to have just one of these risk genes, one of these copies of the risky form, it goes down quantitatively but has a very small effect.

This is true for both these genes, they look very similar and if you put them together they seem to just add up. So, again, I'm sorry about this table, I tried to do something clever with it, to make it more interesting plot but failed to more miserably but essentially here is somebody who has not got the risk version at all. They have got a spot on averaged long word repetition score and you can trace along and say, "These are people that have one copy of the risk form of this gene, two copies and in this direction it's this other gene."

You put them all together, these are people who have got the maximum risk and so this is the amount of difference when you put the two together, they seem to add up. Notice that this is a very different view of genetics from, let's find the gene and it's also going to make it very complicated, trying to give people any sort of genetic counselling about risks because we are talking about tiny effects, that many of us will walk around and have these risk forms, without suffering any obvious ill effect.

It fits in with the fact that when we test parents on things like long word repetition, we often find people who are not aware that they have any problems at all but are actually somewhat down on long word repetition but since nobody is really required to go around repeating long words in every day life, they are not really suffering for it. It's only when you have that in conjunction with other things that you're in trouble.

So, really I have come around many circles in my work in this field, where I have to confess, I started out thinking, "I want to find the cause of SLI," and I imagined that we would find perhaps a psychological cause or a cognitive cause, some sort of thing these children couldn't do, some auditory deficit that would explain their problems, that we would try and fix and it would be linked to a single gene. The only comfort I get for the fact that it's much more complicated, is that so are most other thing that are common in everyday life and the same problems are confronting people working common everyday diseases, like diabetes and heart disease.

So, in a sense, the conditions I'm working on, are in line with those in terms of the pattern that we're finding. So, it does support the notion that language involves multiple processes but I think

that we should probably give up looking for a single course. There might be the odd child where you can track their problems to a single cause but for most of these developmental disorders, it's actually much more complicated than that. Perhaps that's in part because if one thing goes wrong, or isn't quite optimal, language is remarkably resilient function and usually survives anyway.

Well I think I've spoken long enough. If any of you want to check out the background of this work, there will be some references on my website, as well as lots of downloadable papers on this topic but meanwhile I'm very happy to take questions. Thank you.
