KEY TERMS IN AUTISM AND AUTISM SPECTRUM DISORDER RESEARCH

Introduction

This document describes some of the most important ideas in modern day research on autism. It is intended to help people, and especially parents, who may be neither doctors nor scientists to understand better what research might offer their children. For the sake of convenience, the term "autism" is used to cover the whole of autism spectrum disorder or ASD.

1. Genes

Genes are the messages in the cells of the body, coded in the DNA, that decide what proteins are made, when they are made, how much of each is made and where they are made. This is sufficient to make all the different tissues in the body and define their functions. We get our genes from our parents, but a mixing process ensures that no two siblings have exactly the same genetic makeup unless they are identical twins. Apart from these rare individuals, everyone else has minor differences in their genes, and the more distantly related people are the greater the number of differences between them. The vast majority of these variations are harmless and make each one of us unique. However, some genetic differences are responsible for causing disorders or increasing susceptibility to disorders.

Genetic basis of autism

Autism runs in families so that the chance of a child developing autism is higher if his or her family has a history of the disorder. The closer the relation of the child to another affected family member, the greater the chance. The fact that autism runs in families could be a result of common environmental factors, but the evidence strongly supports the idea that autism risk is linked to variations in a number of different genes that somehow interact to make autism more likely. This means that the genetic basis of autism will not be exactly the same for all affected individuals so there may be several types of autism. Since each variation of the gene contributes only a small proportion of the increased risk by itself, it is very difficult to discover which genes are involved. This contrasts with illnesses such as cystic fibrosis which is a disease caused by variation in a single gene. Because only a single gene is involved, it was discovered many years ago.

Methods for genetic analysis

Finding the genetic basis of autism involves examining genetic material from the cells of large numbers of individuals both affected and unaffected by autism. Since unrelated individuals will have thousands of genetic differences, the problem is sorting out the wood from the trees. Consequently, twin studies and sibling studies are valuable because the number of genetic differences between affected and unaffected family members is smaller than in the population as a whole and a higher proportion of these will be linked to autism.

What use is genetic analysis?

If we are successful in finding which genes are involved it may help us develop tests for autism. It may provide the basis for distinguishing between different types of autism at a very early age so that the best treatment can be put into practice. Some genetic variations may indicate a risk of developing autism which will only occur if other factors come into play. Such knowledge could stimulate the use of early educational approaches, visual representation of the curriculum, communication therapy, sensory/occupational therapy and behavioural therapy, and where necessary, the careful use of medicines, in order to improve the outlook for a child. An understanding of the genetic changes involved could also lead to new ideas about the causes of autism and to the development of new and better treatments. Sadly,

experience has shown us that even in genetically much simpler diseases, understanding does not lead quickly or even inevitably to effective treatments. However, without this information, treatments are much less likely to be discovered so it is essential that this work is carried out.

2. Environment

Many or maybe most disorders seem to be caused by a combination of internal genetic factors and external factors that are collectively called environmental. Heart disease runs in families but environmental factors also play a big part – lack of exercise, bad diet and smoking, for example. The role of environmental factors in autism is less clear and has been hugely controversial – among the factors proposed at various times have been maternal deprivation, the MMR vaccine, dietary factors, mercury in vaccines, and infection.. There are also environmental influences in pregnant women that can increase the chances of an autistic child (birth difficulties, age, medication for epilepsy). While many of these have been found to be without a basis in fact, it is likely that there are some environmental factors involved, although to attribute the cause of autism to any one of these is far fetched.

Identification of environmental factors

Finding these environmental factors is not easy. It is the interaction between these factors and the genetic makeup of the individual child that determines how important they are and how sensitive the child is. One method is to look at the effects of potential culprits on the development and function of the brain in experimental animals. Of course animals don't develop human autism but animal behaviour is rooted in the same brain circuits that are involved in human behaviour. So animals can show aspects of autism that could help find these environmental factors and perhaps guide us to methods to counteract their effects.

What use is identifying environmental factors?

The obvious use is to remove or reduce these factors from the environment once they have been clearly shown to increase susceptibility. Where this isn't practical for everyone, it may be possible to remove them from children at risk – for example those with a family history of autism or those whose genes identify them as being particularly sensitive to an environmental factor.

3. Imaging

There are different types of brain imaging that tell us different things. "Traditional" magnetic resonance imaging (MRI) shows us the general structure of the brain. It can show up areas of damage or loss of brain tissues in injury or following stroke. It can show abnormalities such as brain tumours. But it doesn't tell you about how the brain is working. "Functional" MRI (fMRI) does just that as it identifies those parts of the brain that are working harder than others. When they do, they need oxygen, just like muscles do when you exercise, and this is what fMRI shows. So imaging can tell whether some areas are under or overused in people with autism and tell us something about what's going on. Other imaging techniques can show up the intensity and location of some of the important proteins in the brain which are involved in neuronal function. Yet others can show the connections between one part of the brain and another. New developments are coming fast in this area.

What use is imaging?

Imaging increases our understanding of what's going in the brain. Already fMRI has shown us that the brains of people with autism don't respond to external influences in the same way as most other people. Particular parts of the brain seem to be

affected while many others are perfectly typical. So imaging could be useful in early detection and diagnosis, and in telling us about the functional differences between different types of autism. It could help explain the functional consequences of the genes involved in autism risk and help with selecting the right treatment. Understanding the changes in the brain could also give us ideas about developing new treatments.

4. Post-Mortem Brain Research

Imaging methods still do not show the detailed organisation of the brain and studies on post-mortem brain tissue are very important for this. Functional changes shown by imaging may be related to microscopic changes in brain structure. These kinds of studies can also reveal whether there are changes due to disease or past injury, or as a result of genes contributing to autism.. Post-mortem brain tissue can also be used to look at which genes were active in the patient brain and where they were active (we call this "gene expression"), and at the levels and distribution of proteins that are important in brain function ("protein expression")

What use is post-mortem brain research?

Better understanding of the microscopic changes in brain structure that result in autism and relating these to the differences in gene and protein expression could help us understand what is going on at a level of detail that could point to new ideas about treatments, most likely involving medicines that could reverse or counteract the changes. Brain imaging is marvellous for seeing the big picture but it is impossible to translate what we see into the chemical processes involving proteins that are the basis of all medicines.

What are brain banks?

Brain banks are incredibly important for this kind of work. Like money in high street banks, brains are deposited in a brain bank after someone has died. The brain tissue is frozen or preserved, catalogued with the medical history of the patient and then made available to qualified scientists and doctors to do research. Brain banks are maintained under the strictest ethical guidelines by major institutes (e.g. universities and hospitals) and are often created by patient organisations, particularly those supporting rare diseases for which the availability of research material is limited. One of the most well known in the UK is the London Brain Bank for Neurodegenerative Diseases which also contains brains from people with autism.

Why are Brain Banks needed?

Brain banks, such as Autism Speaks' Autism Tissue Programme, represent a concerted and dedicated effort to collect post-mortem brain and brain tissue from individuals affected by a particular disorder and thereby establish a centralised resource for scientists. This ensures best use, best practice and sharing of this scarce and precious material. Concentrated efforts to develop a brain bank are particularly important for less common brain disorders such as autism since building this type of resource is costly and often beyond the capabilities of individual research groups. Also if the collection brain after death is performed uniformly it is possible to standardise the type of information gathered about the brain donor such as the medical history and this is valuable in helping interpret the research findings.

5. Omics

Omics is a strange term used to describe a collection of new research methods that are becoming increasingly important in diagnosis and treatment. These are genomics, transcriptomics, proteomics, metabolomics and lipidomics. If all are being used, we talk about a "multiomics" approach. Strictly genomics is just the study of genes and that was covered in section 1. Sometimes the term

"functional genomics" is used to describe generally what the genes do, but we have the individual "omics" words above to describe gene function in more detail. A brain cell, a kidney cell and a heart cell all have the same genes but what makes them different is which genes are active and turned on (or "expressed") and to what extent. The first result of the activation of a gene is the manufacture of a "transcript" and the study of transcripts is called transcriptomics. Transcriptomics measures which genes are activated and by how much and with new techniques it is quite routine to look at tens of thousands of different genes at a time. The same methods can look at the differences between individuals with and without autism and see the effects of genetic differences on the expression of the genes. But most genes just make proteins, so why not look directly at the proteins? This is the study of proteomics, but it's not as easy as transcriptomics. Proteins are more difficult to handle and analyse and aren't preserved as well in tissue from brain banks. However proteomics can be applied to blood samples and to the cerebrospinal fluid (the liquid that bathes the brain and spinal cord and can be sampled by lumbar puncture) and so can be applied to the living. Metabolomics is the analysis of the metabolites in the body, the chemicals derived from the breakdown (metabolism) of sugars, fats and proteins. Lipidomics is the study of the fats (lipids) themselves. In the same way that the protein patterns are a measure of gene expression, the metabolite and lipid patterns or signatures are a measure of the actions of proteins.

Methods used in omics

Omics is still developing as a science which is why its use in diagnosis and treatment is still in its infancy. The machines used to screen the expression of tens of thousands of genes or analyse thousands of proteins and metabolites are highly specialised and very expensive, and they exist only in the research labs of top universities and industries. You will probably never find these machines in your GP's or specialist's surgery but once the complicated analyses are done and the wood has been sorted from the trees, the hope is that much simpler instruments will be designed that will be able to test for the presence of specific factors in blood which are linked to autism. These machines and their use could become routine in surgeries and hospitals.

What use are omics?

The gene expression pattern, the protein pattern and the metabolite signature all result from the interaction between your genes and your environment. But as you move from the genes themselves through gene expression to proteins and then to metabolites you are moving from analysing only what you inherited to looking increasingly at the influence of the environment on your bodily function. For example, genetic analysis might tell you about which people are predisposed to diabetes. Analysing gene and protein expression will tell you whether their genetic background is causing diabetes, and measuring glucose (a metabolite) will tell you how they are responding to their last meal and is the basis of the diagnosis of diabetes. There is no reason why this should not also be true for autism; it's just that we have not made as much progress yet. We are learning more about the genetic factors involved in autism. What we need now are methods that can be used by the medical profession to tell them about what kind of autism the child has, what treatments should be prescribed, what treatments are being effective, and what the child's future prospects are. These are some of the things that we hope imaging will help provide, but they are also within the realms of possibility for the future development of omics. Much work needs to be done before this becomes a reality.

6. Drug treatments

People with autism are often prescribed medicines to help them cope with some of the difficult aspects of their conditions. There are no medicines for the treatment of autism itself for many reasons. It's not a single condition for one. We don't understand much about what is going on in the brains of people with autism and what causes the condition. Consequently there is no logical and scientific basis for the design of specific treatments. We also need to be very cautious. Administering drugs to young people whose brains and bodies are still developing is not something to be undertaken lightly. Consequently, current drug treatments are those that have been tried and tested for other conditions, but have been found to be useful for some of the common distressing aspects of autism. Frequently these are described as co-morbidities, that is, conditions that are not believed to be core symptoms of autism itself, but are commonly found in conjunction with autism. Whether they are truly co-morbid in the sense that they are separate conditions, or whether the one results from the other, is probably not important with our current state of knowledge. What is important is that every person should receive the best possible support for their condition.

What kinds of drugs are used?

Ritalin is commonly prescribed when the child has co-morbid attention deficit hyperactivity disorder (ADHD). Risperidone can be used to reduce repetitive or persistent behaviour - such as obsessive-compulsive disorder, tics or Tourette's syndrome - and also to reduce destructive behaviour and self-harming. The drug has been approved in the US for autism with hyper-irritability, the first time a drug has been specifically approved for treatment of autism. When doctors see these conditions to be a result of a child's autism, there seems to be a greater reluctance to prescribe medication than if the child has a primary diagnosis of ADHD or Tourette's for example. Antidepressants (SSRI's) are prescribed to reduce anxiety, and to make people calmer and less aggressive. In higher functioning autistic children and adolescents, depression is quite common and can be treated with the same medications. Epilepsy is very common in the autistic population, as it is in other developmental conditions, and is treated with a variety of anticonvulsant drugs. The incidence of bowel disease in autistic children has been a topic contributing greatly to the fierce debate about the causes of autism. Whether or not disease rates are really higherr, it remains a fact that autistic children often have problems with food – a general dislike or a narrow range of foods that are enjoyed, sensory hypersensitivity, increased anxiety. All of these may contribute to diarrhoea or constipation which can cause great pain and distress. This may contribute hugely to their disturbed behaviour but it can go undiagnosed in non-communicative children. Recognition and treatment can really transform some children's lives.

How are new drugs discovered?

This is a long, complicated and expensive process of trial and error, but one based these days on the need to understand exactly what causes a particular illness or condition. Of course this makes discovering new medicines for autism very difficult because we do not know the causes or exactly what is going on in the brains of people with autism. The kinds of new science described above will eventually lead us to understand these things better. With that knowledge we will have a much greater chance of developing medicines that address the core symptoms of autism. But there are no guarantees that this will happen or that these new medicines will be truly effective.

What use will new drugs be?

Even if miracle cures are something for the far future, we will see over the next few years improvements to the kinds of drugs presently used to treat the co-morbid conditions. Even with existing drugs, there are opportunities to find better ways of dosing children to make it easier on them and on parents and carers to stick to the

treatment. We will see new medicines that are more effective, that are safer (especially in children) and that have fewer unpleasant side-effects. We will also see better diagnostic methods that will identify different types of autism and their response to medicines, as well as better recognition of treatable co-morbid conditions (such as bowel problems for example). This will help direct the right treatment much earlier than we can nowadays, and making autistic children feel healthier will be tremendously valuable for their education.

7. Educational methods

Education remains at present the most powerful method for helping people with autism. As a result it also leads to the over promotion of some educational approaches as superior to others or even providing a "cure" for autism. People with autism are not all alike and no one method is likely to bring about profound improvement let alone a cure. The best methods are those that work with children's strengths and with appreciation of their characters to help address their weaknesses. Autistic children struggle with language so visual learning is appealing to them. They are frequently anxious, so methods that provide structure and make them feel in control can alleviate their worries. They have huge sensory sensitivity issues which impede learning and contribute in a major way to their problems with behaviour and social skills.

What methods are useful?

These are just examples of methods that are useful because they are rooted in an appreciation of the issues facing autistic children. TEACCH (Treatment and Education of Autistic and Communication Handicapped Children) is widely used to provide a structured environment with visual clues and cues to help a child understand what is expected of them at any time. It helps them to engage in independent work, thereby increasing their sense of self-esteem in themselves as learners. It provides them with their own space in which to deal with anxiety and for the introduction of new skills, and helps them manage transition and change, things that typically are very difficult for autistic children. PECS (Picture Exchange Communication System) is a visual communication system useful for children with or without language. For the latter group it can be a route to the eventual acquisition of language. For both groups, simplicity of communication through pictures reduces anxiety, improves their communicative abilities, and builds understanding of more complex language. It uses functional analysis and leads children to a point where they are able to initiate conversation and to comment on the world around them. ABA (Applied Behavioural Analysis) is a method to teach behaviours to autistic children through a process of observation, positive reinforcement and prompting, often breaking each skill into small units. Generally, it's an intensive process requiring trained therapists and many hours a week spent in ABA therapy. It is also clear that Early Intensive Behavioural Intervention, which is not necessarily the same as ABA, is very helpful. Schools that have nurseries and can offer EIBI argue that they can teach discrete skills and their generalisation, whilst also teaching and encouraging social skills. Everyone agrees that early intervention is really important for children to progress.

What's needed?

What is needed is objective research on the efficacy of different teaching methods. The enthusiasm of the advocates of one method can sometimes blind them to its disadvantages and to recognition of the usefulness of other methods. Autistic children grow and develop and their needs change as they get older. All autistic children are different and their parents/carers are entitled to a proper analysis of what is available, what is best suited to their children and how their education needs to evolve with time to maintain benefit. The permanence of the effect of strongly interventional methods needs assessment. Do methods aimed primarily at language acquisition or behaviour, for example, improve children's social skills, and their ability to tolerate and mix with others? Some areas seem woefully underserved.

The issue of sensory sensitivity, its causes and treatment, is poorly appreciated, but it has a huge impact on the suitability of particular educational approaches.